Behavioral Aspects of Heart Disease

Chest Pain and Angiographically Normal Coronary Arteries

Implications for Treatment

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Approximately 20% to 30% of patients who undergo coronary arteriography for the evaluation of chest pain are found to have normal coronary arteries. These patients have a survival rate comparable to that of the normal population, yet they continue to complain of symptoms on extended follow-up, and about half of this group are disabled on account of chest pain. Once other clinically obvious disorders have been ruled out, common diagnostic considerations include microvascular angina, esophageal dysfunction, and perhaps fibromyalgia. Panic disorder, however, is the most common condition affecting these patients and can be diagnosed in at least one third of the group, with or without the presence of the other conditions mentioned. Appropriate diagnosis and treatment can reduce the psychosocial morbidity so frequently seen in these patients. ***(Texas Heart Institute Journal 1993;20:170-9)***

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Coronary arteriography is recommended for patients with chest pain when the diagnosis of coronary artery disease remains uncertain after noninvasive testing or when it is clinically important to obtain accurate definition of the coronary anatomy. In most cases, arteriography will provide the necessary information to decide on the course of therapy. However, in some cases the arteriogram will reveal normal coronary arteries. In their clinical presentation, patients with angiographically normal coronary arteries may be indistinguishable from patients with coronary artery disease.[1] They present a diagnostic enigma that even the scientific technology available today has not solved.

Historical Background

William Heberden[2] the elder first described the symptoms of angina pectoris in a paper titled "Some account of a disorder of the breast," which he presented at the Royal College of Physicians and later published (1768). Soon after Heberden's description of angina, Edward Jenner,[3] the discoverer of the smallpox vaccine, made a postmortem observation of coronary occlusive disease in a patient who had died after exhibiting chest pain.

While chest pain came to be recognized as a symptom of serious heart disease, with all its implications, physicians noted over the years that some patients with chest pain had no identifiable heart disease or any other obvious physical explanation for their symptoms. Documentation of this problem can be found in the writings of Laennec,[4] Corvisart, and Testa,[5] and in observations made on British soldiers in India and the Crimea.[6] In 1871, Jacob Mendes Da Costa, a Philadelphia physician of great eminence in his time, published a comprehensive article on this subject in the *American Journal of the Medical Sciences*.[7] Da Costa made his observations on soldiers of the American Civil War: "Shortly after the establishment of military hospitals in our large cities, I was appointed visiting physician to one in Philadelphia, and there I noticed cases of a peculiar form of functional disorder of the heart, to which I gave the name of irritable heart—a name by which the disorder soon became known both within and without the walls of the hospital." The symptoms described were primarily chest pain, dyspnea, and palpitations.

Irritable heart, or Da Costa's syndrome, became an established clinical entity. The diagnosis was commonly applied to soldiers with chest pain during the

Franco-Prussian War and the Boer War in the 1890s. During World War I, British physicians referred to this disorder as "soldier's heart," and the *British Medical Journal* of 1916 contained 39 papers on the subject. Sir Thomas Lewis[8] summarized his experience with 1,000 soldiers with this condition, and used the term "effort syndrome." In the United States, Oppenheimer and colleagues[9] introduced the term neurocirculatory asthenia in 1918. Others have preferred terms such as disordered action of the heart,[10] hyperkinetic heart syndrome,[11] hyperdynamic beta-adrenergic circulatory state,[12] cardiac neurosis, and autonomic imbalance. In 1941, Paul Wood wrote an extensive review of the subject that appeared in 3 parts in 3 consecutive issues of the *British Medical Journal*.[13] Wood felt that the term Da Costa's syndrome was the most appropriate, since it avoided "references to the heart, the circulation, to effect or to false or unproved mechanisms." He gave a detailed account of symptoms and signs in 200 cases. Left-sided chest pain occurred in 78%, dyspnea in 93%, and palpitations in 89%. Other frequent symptoms were fatigue, diaphoresis, nervousness, and dizziness. Wood concluded that "the evidence demands that Da Costa's syndrome be regarded as an emotional reactive pattern" and cautioned: "no greater blame can be attached to a psychiatrist who fails to make a physical examination than to a physician who fails to probe the mind."

Over the years that followed, physicians continued to search for a possible explanation for chest pain in these patients. A link between hyperventilation and chest pain was reported.[14,15] With the availability of echocardiography, conditions such as idiopathic hypertrophic subaortic stenosis and mitral valve prolapse could be more easily identified. With the advent of coronary arteriography in the 1960s, it became possible to ascertain with considerable accuracy the severity and distribution of coronary artery disease in the living patient. But the problem persisted: cardiologists noted that a certain percentage of their patients undergoing coronary arteriography for angina-like chest pain were found to have clear coronary arteries. In most cases, no cause of their pain could be demonstrated. In 1967, 2 reports appeared concerning the paradox of anginal chest pain in the absence of coronary artery disease.[16,17] Since then, some have referred to the condition as Gorlin-Likoff syndrome (after the names of the authors).[18] Arbogast and Bourassa[19] performed right atrial pacing on a group of patients with chest pain and angiographically normal coronary arteries (Group X), and compared the findings with those from a group of patients with known coronary artery disease (Group C). They noted that patients in Group X exhibited enhanced left ventricular function during pacing stress, a response clearly different from that of patients with coronary artery disease. Kemp[20] referred to the condition as syndrome X, and observed that a major problem of studies on syndrome X may be "the assumption of homogeneity of cause in all subjects. It seems unlikely that a syndrome defined by the presence of chest pain and the absence of coronary artery disease would have a unique etiology."

Prevalence

The percentage of arteriograms showing normal coronary arteries varies among regions, hospitals, and operators. Generally, 20% to 30% of patients undergoing coronary arteriography for the evaluation of chest pain are found to have normal or near-normal coronary arteries.[21-23] As an example, 25% of patients screened for the Coronary Artery Surgery Study (CASS) had normal or slightly abnormal coronary arteriograms.[24] In a smaller series of 706 consecutive patients who underwent cardiac catheterization because of symptomatic chest pain, Bertrand and colleagues[25] found the incidence of normal coronary arteriograms to be as high as 89% in patients with atypical angina and 29% in patients with typical angina. In the same study, among 395 patients with nonsignificant coronary stenosis on arteriography, 221 (56%) had presented with atypical angina, 93 (24%) with rest angina, and 81 (21%) with exertional angina in the absence or presence of rest angina. In the United States, more than 1 million cardiac catheterization procedures are performed annually for the evaluation of chest pain;[26] it can be inferred that 200,000 of these show normal coronary arteries.

Prognosis

Several studies have shown that the syndrome of angina with normal coronary arteries carries a favorable prognosis for longevity. Proudfit and associates[27] performed follow-up on a series of 521 patients for a period of 10 years. The patients were divided into 3 groups, in accordance with early coronary arteriographic results: 357 had normal results, 101 had mildly abnormal results (<30% narrowing), and 63 had moderately abnormal results (30% to 50% narrowing). Coronary events occurred in 2.1% of patients with normal arteriograms, in 13.8% of those with mildly abnormal arteriograms, and in 33% of those with moderately abnormal arteriograms. Isner and coworkers[28] performed follow-up on a group of 121 patients with angiographically normal or near-normal coronary arteries for 1 to 11 years (mean, 4.3 years). They noted a 2.5% incidence of sudden death and a 3.4% incidence of acute myocardial infarction. The CASS registry[29] shows a 7-year survival rate of 96% in patients with normal coronary arteriograms. These figures indicate a favorable prognosis for longevity in such patients.

Despite the excellent prognosis for survival, most patients with chest pain and normal coronary arteries suffer considerable disability. Ockene and associates[30] conducted follow-up on a series of 57 patients with angiographically normal coronary arteries for periods ranging from 6 to 37 months. They noted that 70% of the patients continued to experience chest pain, 47% said their usual daily activities were limited by chest pain, and 51% said they were unable to work because of their symptoms. Forty-four percent continued to believe that they had heart disease, although their overall use of medical facilities had decreased. In a similar study, Lavey and Winkle[31] performed follow-up on 45 patients with chest pain and normal coronary arteriograms for a mean period of 3½ years. During follow-up, 79% of those whose activities initially had been limited by cardiac symptoms continued to be limited to the same degree or more. Eight-two percent continued to see physicians because of cardiac complaints. For a mean period of 6.3 years, Papanicolaou and coworkers[32] conducted follow-up on 1,977 patients with chest pain and normal coronary arteries or insignificant coronary artery disease. Seventy percent of these patients continued to experience chest pain, and 50% were unable to exert themselves. The demonstration of anatomically normal coronary arteries produced no relief in chest pain or symptom-related morbidity for most of the patients.

One probable advantage of cardiac catheterization in these patients is a decrease in the re-hospitalization rate. Several studies have reported that the re-hospitalization rate for chest pain complaints in these patients ranges from 3% to 27%. In Faxon and colleagues' series[33] of 72 consecutive patients with chest pain and normal coronary arteries, only 24% became pain free after the procedure. However, hospitalization for all patients decreased considerably, resulting in a notable decrease in estimated hospital costs.

It is obvious that the catheterization procedure is not "therapeutic" for this group of patients, and that reassurance is usually unsuccessful in relieving symptoms. As the patient continues to complain of chest pain, the cardiologist may consider repeating coronary arteriography. After a mean interval of 42 months, Marchandise and associates[23] repeated coronary arteriography in patients with nonsignificant coronary artery disease, noting no development of coronary artery disease in patients with initially normal arteriograms. However, among patients with less than 50% stenosis of a least 1 major coronary artery, 27% showed progression of the disease. These data suggest that patients showing minimal irregularities in their coronary vessels may in fact need to be reassessed by a cardiologist if symptoms persist. But repeating cardiac catheterization in a patient with a totally normal coronary arteriogram is unlikely to yield new data and may subject the patient to unnecessary risk. As an extreme example of the risk involved, Shah and coworkers[34] reported a patient with Münchausen syndrome and normal coronary arteries, who underwent repeated cardiac catheterization leading to the loss of a limb.

Etiology

The chest pain in patients with normal coronary arteries may be of cardiac or noncardiac origin. The cardiac causes commonly considered in the differential diagnosis of these patients include Prinzmetal's angina, pericardial disease, and mitral valve prolapse. Except for coronary artery spasm, these causes usually can be identified with ease in the clinical setting. In particular, the widespread availability of echocardiography has made relatively simple the diagnosis (before catheterization) of mitral valve prolapse and idiopathic hypertrophic subaortic stenosis. The noncardiac causes of chest pain commonly considered in these patients are esophageal disorders, rheumatic, pulmonary, and (occasionally) abdominal disease. Among these, esophageal disorders are frequently the most difficult to recognize and establish as the cause of a patient's discomfort. In addition to the conditions mentioned above, a number of other possible causes, cardiac and noncardiac, have been suggested to explain the chest pain in these patients; they are discussed later. The increasing evidence that psychiatric conditions, particularly panic disorder, can be diagnosed frequently in these patients has important therapeutic implications.

Cardiac Causes. The chest pain in patients with normal coronary arteriograms cannot be explained on the basis of false negative or misread angiograms. It is well established that coronary arteriography is a highly accurate method of evaluating the morphology of both normal and abnormal coronary vessels.[35,36] Moreover, patients with chest pain and normal coronary arteries have been shown to have a mortality rate comparable to that of the normal population and clearly lower than that of patients with coronary artery disease. At the same time, it is important to remember that an apparently normal arteriogram may be seen in a patient with coronary disease limited to the ostium.[37] This uncommon condition, readily identified by a skilled angiographer, carries a poor prognosis without proper therapy.

Coronary artery spasm is a frequent consideration in patients with chest pain but angiographically normal coronary arteries. The diagnosis, although elusive, may be accomplished with the observation of the characteristic ST-segment elevations during episodes of chest pain. To induce arterial spasms, ergonovine can be infused.[25] In several studies of patients with chest pain and angiographically normal coronary arteries, ergonovine testing was used to ex-

clude patients with Prinzmetal's angina.[25,38] Ergonovine testing usually yields negative results in this group of patients;[39-41] it is estimated that the overall prevalence of Prinzmetal's angina in patients with chest pain and normal coronary arteries is less than 10%.

Myocardial bridging can be demonstrated in some patients with angiographically normal coronary arteries, but this is an unlikely cause of chest pain.[42] Several studies employing treadmill testing and thallium scintigraphy have failed to demonstrate ischemia in patients with myocardial bridging.[42,43]

Chest pain in drug abusers is a problem of particular concern today. Cocaine and its non-ionic complex form called "crack" are potent vasoconstrictive agents.[44,45] According to estimates, more than 5 million people in the United States are occasional or regular users of cocaine.[46] In 1987, 1,700 cocaine-related deaths were reported to the National Institute of Drug Abuse.[47] The mechanism of cardiovascular toxicity is not clearly understood. Cocaine has been associated with an increase in circulating catecholamines, which can provoke tachycardia, hypertension, and local vasoconstriction.[48,49] About 15% of cocaine users experience acute chest pain.[50] Myocardial infarction, presumably the result of coronary spasm in susceptible individuals, can result in sudden death.[49,51] Coronary arteriography usually shows normal coronary arteries.[49,51] Therefore, in the appropriate setting, drug abuse should be considered in the differential diagnosis of patients with chest pain and normal coronary arteries.

Some researchers have proposed a variety of other mechanisms involving the heart, in the attempt to explain the chest pain in patients with normal coronary arteries. Generally, such patients do not show perfusion defects on thallium scintigraphy, but a number of them, in response to exercise, do show abnormal ejection fractions by radionuclide ventriculography.[52-57] In order to evaluate myocardial perfusion and reserve in patients with chest pain and normal coronary arteries, Geltman and colleagues[58] performed positron emission tomography before and after intravenous dipyridamole administration, and compared the findings with those from a control group of normal subjects. Eight of 17 patients with chest pain had an abnormal myocardial perfusion reserve, and these 8 patients had significantly higher perfusion at rest than did normal subjects. Abnormal lactate metabolism has also been proposed as a possible cause of chest pain in these patients.[59,60] Currently, it appears as though these findings may reflect an abnormality in the coronary microvasculature (100 to 500 microns in size) not revealed by coronary arteriography.

Cannon and coworkers[61] have suggested that some patients with chest pain and normal coronary arteries may have inappropriate coronary arteriolar or small coronary artery constriction with abnormal vasodilator reserve. They measured great cardiac vein flow, coronary resistance, and coronary sinus lactate levels at rest and with pacing, and they subjected the patients to intravenous ergonovine and dipyridamole infusions. They noted that in these patients the great cardiac vein flow remains lower than normal with atrial pacing in the control state, as well as after ergonovine or dipyridamole administration. On the other hand, coronary resistance tends to remain higher than normal in these patients. On the basis of these observations, Cannon and coworkers[62] have proposed a model for microvascular angina or apparent effort angina without obvious cardiovascular pathology.[62] In microvascular angina, the major epicardial coronary vessels seen on arteriography are normal. However, there are fixed anatomic or functional blockages within the walls of the pre-arteriolar coronary segments. Because of these blockages, the smooth muscle surrounding subendocardial vessels remains widely dilated in the resting phase. With exercise, the subepicardial vessels dilate, but the subendocardial vessels are unable to dilate any further, resulting in myocardial ischemia. The theoretical concept of this model is attractive, but the supporting evidence needs confirmation.

Several researchers have actually attempted to demonstrate small-vessel disease by histopathologic studies. Initial studies performed by Opherk and colleagues[63] yielded negative results. More recently, Mosseri and co-workers[64] reported endomyocardial biopsy results on 6 patients with angina and normal coronary arteries, noting fibromuscular hyperplasia, hypertrophy of the media, myointimal proliferation, and endothelial degeneration involving the small coronary arteries. The importance of these findings remains unclear, particularly since several patients in this study had hypertension. Mosseri has suggested that small-vessel disease should be suspected when a patient with angina is found to have slow flow of the angiographic contrast medium despite large, patent arteries.

Noncardiac Causes. Esophageal disorders may account for chest pain in some patients with angiographically normal coronary arteries.[65] Esophageal chest pain is commonly caused by esophageal reflux or by motility disorders such as nonspecific esophageal motility disorder, "nutcracker" esophagus, and hypertensive lower-esophageal sphincter. Upper gastrointestinal radiology, upper endoscopy, the Bernstein test (intraesophageal acid perfusion), esophageal manometry, and pH monitoring have been used to investigate these patients for esophageal disorders.

The overall prevalence of esophageal disorders is estimated to be 18% to 58% in patients with chest

pain and normal coronary arteries.[66-71] However, these data showing the apparently high prevalence of esophageal dysfunction in patients with chest pain and normal coronary arteries are of questionable significance when weighed against data revealing a comparable prevalence of esophageal disorders in other populations. For example, Areskog and Tibbling[72] reported esophageal dysfunction in 33% of patients after acute myocardial infarction, while Spandow and associates[73] found incompetence of the lower esophageal sphincter in 28% of a group of subjects selected at random. Provocation testing with edrophonium or other agent is commonly used to induce spasm in patients studied, but patients usually do not report chest pain even when the test is positive.[66] In contrast, Hewson and colleagues[74] have demonstrated acid reflux as a probable cause of chest pain in about 50% of these patients, based upon their symptoms' occurring coincident with reflux. Their study suggests that reflux may be the common cause of esophageal abnormalities noted in patients with noncardiac chest pain and that 24-hour esophageal pH monitoring may be the best test for evaluating these patients.

Rheumatic disorders have been known to cause chest pain. Costochondritis is readily diagnosed on clinical examination and is uncommon in patients undergoing coronary angiography. More recent observations suggest that fibromyalgia may be a common disorder in patients with noncardiac chest pain, occurring in about 30% of the group.[75] Myers and associates[76] have described an uncommon condition termed "cervicoprecordial angina," which causes substernal chest pain similar to angina pectoris but is caused by cervical root compression.[76]

Another intriguing suggestion put forth by some researchers is the presence of a hematologic abnormality in these patients. Eliot and Bratt[77] have reported abnormal hemoglobin-oxygen dissociation in patients with chest pain and normal coronary arteries, as manifested by a marked elevation of the half-saturation point and by a reduction of Hill's constant. However, Vokonas and associates[78] were unable to reproduce these results in their series of patients. Preston[79] suggested enhanced platelet aggregation as a possible cause for the chest pain, but Rao and coworkers[80] reported increased antithrombin III activity in these patients, in comparison with coronary artery disease patients; this same comparison showed no significant difference in platelet volume, platelet aggregate ratios, prothrombin time, partial thromboplastin time, nor in plasma levels of fibrinogen or coagulant factors V and VIII. Consequently, the hematologic theories have remained unconfirmed.

In 1628, William Harvey wrote, "Every affection of the mind that is attended with either pain or pleasure, hope or fear, is the cause of an agitation whose influence extends to the heart."[81] Yet, physicians over the years have tended to overlook psychiatric causes of chest pain, out of concern for the consequences of misdiagnosing a physical condition such as coronary artery disease by calling it a psychiatric problem. Now, however, that coronary arteriography is in wide use and that patients with normal coronary arteries have been shown to have a normal mortality rate, it is imperative to consider psychiatric evaluation of some of these patients in an attempt to reduce psychosocial morbidity. The possible psychiatric causes of chest pain include panic disorder, generalized anxiety disorder, agoraphobia and other phobias, depression, somatization, conversion, malingering, and Münchausen syndrome.[82] Our observations suggest that, except for panic disorder and generalized anxiety disorder, other conditions are uncommon in this group of patients.[83-85]

Panic disorder as a distinct subtype of anxiety affects only 2% to 5% of the general population; however, among cardiology patients the prevalence ranges from 10% to 14%. It appears that panic disorder and angina pectoris may be easily confused in differential diagnosis, because the 2 conditions have certain symptoms in common. Moreover, panic attacks (unlike chronic anxiety states) are time-limited and follow a distinct pattern similar to that of anginal attacks, with symptoms that rapidly attain peak intensity and then subside within a few minutes.

In a retrospective review of 123 consecutive patients with chest pain and normal coronary angiograms,[83] we found that one third had at least 4 panic symptoms, suggesting that many of these patients may in fact be suffering from panic disorder. We then undertook a prospective study[84,85] to evaluate the prevalence of panic disorder in these patients. Patients undergoing cardiac catheterization for chest pain were included in the study when they were found to have less than 30% stenosis of all major vessels. Excluded were patients with any coronary lesion causing stenosis exceeding 30%, patients with any other type of heart disease, and patients with any obvious noncardiac cause of chest pain. For the purposes of our study, standard psychiatric criteria were used in the diagnosis of panic attacks and panic disorder. Each patient completed self-report forms and then underwent a structured clinical interview, administered by a psychiatrist. The diagnosis of panic disorder was made when the subject met the revised DSM-III criteria. Out of 94 consecutive patients interviewed, one third had current panic disorder and another 15% or 16% had panic attacks with a frequency that did not satisfy our criteria for the diagnosis of panic disorder. Additional patients may have had symptom-limited panic attacks. We also found that 38% of our patients with panic disorder had major depression currently or had experienced

it in the past. On the other hand, only 17% of our patients without panic disorder had ever suffered from depression. The major distinction of panic disorder in cardiology patients is that cardiology patients tend to display less agoraphobia.[86] However, there is a good deal of information to suggest that these patients have "effort fear."[87] In other words, they focus on the cardiac origins of their chest pain and therefore avoid exertion in the same way that other phobic patients avoid situations associated with panic attacks. Although the precise mechanism has not yet been defined, it appears that a large number of patients with chest pain and normal coronary arteries may have a treatable psychiatric condition.

Early theories regarding the cause of panic attacks have arisen from the hypothesis that a panic attack is a phobic response (interoceptive phobia) to a "normal" physical sensation. Upon experiencing a specific somatic sensation, the patient predisposed to panic interprets this sensation as an impending heart attack; the fear then accelerates the awareness of the somatic sensation, creating a vicious spiral that leads quickly to a panic attack in which patients with normal coronary arteries experience chest pain. The abnormal esophageal, cardiac, rheumatic, and other findings are consistent with this theory in so far as panic patients could be responding to genuine nociceptive impulses. The crucial difference is that the esophageal, cardiac, and other hypotheses suggest abnormal nociperception, while the interoceptive phobia hypothesis suggests that the sensations are normal.[88] The proposal that patients with chest pain and normal coronary arteries are experiencing nociceptive reflexes is supported by Cannon's finding[89] that many of these patients have increased cardiac sensitivity: chest pain is induced by catheter manipulation in the right heart (particularly in the right ventricle), by intracardiac pacing, and by the selective injection of contrast material into the coronary arteries.

Differential Diagnosis

It appears from current data that the diagnoses most commonly encountered in patients with chest pain and angiographically normal coronary arteries are panic disorder and esophageal dysfunction (reflux, abnormal motility, or both). Microvascular angina as a postulated mechanism of myocardial ischemia in these patients needs further clinical definition. Fibromyalgia is yet another condition that may affect this group. It is interesting to note that considerable overlap exists between these disorders. Cannon and coworkers[90] have reported that 57% of patients with microvascular angina have abnormal esophageal motility, while Roy-Byrne[91] and associates found panic disorder in 40% of patients with microvascular angina. Clouse and Lustman[92] diagnosed psychiatric problems in 84% of patients with esophageal motility disorders. Primary fibromyalgia syndrome has been compared and related to affective disorders, particularly depression.[93,94] It is possible that these disorders are different aspects of a single "chest pain syndrome," although the exact pathophysiologic mechanism linking them is not yet clear. Chest discomfort can involve a complex interaction of somatic and psychological factors interacting to varying degrees in different subjects, and perhaps in the same subject at different times. In investigating patients with chest pain and normal coronary arteries, the physician should attempt to define the relative contributions of the various somatic and psychological mechanisms that may be involved in causing the patient's symptoms.

Management

In the management of a patient with chest pain and normal coronary arteries, the physician should avoid performing unnecessary tests or prescribing unnecessary drugs, partly because this may give the patient the erroneous impression that he or she has a serious undetected illness. Routine ergonovine testing is not recommended for patients with normal coronary arteriograms; however, ergonovine should be considered when Prinzmetal's angina is suggested by the quality of pain or by the association of pain with arrhythmias, but has not been proved by recording ST-segment elevation during symptomatic episodes. All patients with normal angiographic results should be reassured that they have an excellent prognosis in regard to mortality and other serious cardiovascular events. If cardiac causes have been ruled out, the patient should be informed of this finding in clear and certain terms. At the same time, cardiac medications should be discontinued, or the reason for continuing their use should be explained very carefully. Otherwise, the patient could perceive their continued use as a signal opposing the physician's verbal reassurances. Many laymen seem to believe that every pharmacologic agent has but a single specific medical indication. For this reason, if a nitrate (for example) was started for suspected coronary disease and is being continued for esophageal spasm, the physician should clearly explain this to the patient. Because of the long-term psychosocial morbidity of this condition, chest-pain patients with normal coronary arteries should be evaluated at a follow-up visit about a month after angiography. If the patient continues to have symptoms, the physician should consider consulting a gastroenterologist or a psychiatrist, in accordance with clinical suspicions.

The treatment of gastroesophageal reflux may involve lifestyle modification, as well as the use of antacids, H_2-blockers, omeprazole, or even promotility drugs.[95] Esophageal spasm may be treated

with calcium channel blockers,[96,97] nitrates,[98,99] or anticholinergic medications. Surgical therapy has been applied to selected patients with esophageal disease, when all conservative measures have failed.[100]

The diagnosis of microvascular angina may be difficult. The complex invasive testing used by most investigators to date is not practical in the clinical setting. Cannon and his group[101] have recommended a therapeutic trial of a calcium channel blocker as the simplest way of identifying the condition, since most patients with microvascular angina will respond to the drug.[101] Others have suggested use of a β-blocker.[102]

The treatment of panic disorder involves cognitive-behavior therapy and antidepressants. Most antidepressants seem to be effective.[103] Side-effect profile, cost, and co-morbid psychiatric disorders should influence the choice of specific agents. The new selective serotonin-uptake inhibitors (fluoxetine, sertraline, and paroxetine) are effective. They have a low side-effect profile, but their cost is relatively high. Imipramine is the standard to which most other agents are compared. Benzodiazepines may also be useful for panic disorder as initial treatment, and later as needed. Fast-acting benzodiazepines with a short half-life, such as alprazolam and lorazepam, are best suited to abort incipient panic attacks. In prescribing psychotropic medications to this group of patients, it is important to note some of their cardiovascular effects and their interactions with cardiac medications.[104,105] Tricyclic agents and trazodone can block the centrally mediated antihypertensive action of clonidine. On the other hand, postural hypotension may occur with the use of these drugs.[106,107] Tricyclic antidepressants have properties resembling Type I antiarrhythmic agents.[108-110] Electrocardiographic changes reported include reversible prolongation of the P-R, QRS, and Q-T intervals, ST and T wave changes, and development of atrioventricular and bundle branch block. An increase in heart rate by about 10 to 20 beats per minute is common with the use of tricyclics. There have also been isolated reports of sudden death occurring in patients receiving these agents, particularly in the presence of cardiac disease.[111-113] Benzodiazepines in therapeutic doses should not manifest cardiovascular side-effects. However, for patients receiving digoxin, there have been reports of digoxin toxicity with concomitant use of diazepam or alprazolam.[114-116] In general, the prescription of psychotropic medications should be handled by physicians trained in their use.

Patients with chest pain and normal coronary arteries present a diagnostic challenge that requires careful investigation and follow-up. A definitive diagnosis is important before specific therapy for the disorder can be instituted. In formulating a successful treatment plan, the physician must consider the overlap, frequently seen in these patients, between various somatic and psychological mechanisms.

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