Evaluation of Patients With Chest Pain and Normal Coronary Angiograms

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Over 1 million coronary angiograms are performed in North America annually, and a significant number are interpreted as normal. In the Coronary Artery Surgery Study Registry of the 1970s, normal angiograms were found in 19% of patients, and the prevalence may not have changed in the current era of more sophisticated noninvasive testing. A recent study found that 19% of patients had no arteriographic evidence of disease. For women selected for angiography, a normal result is found 3 times more frequently than for men. Further elucidation of the diagnosis in a patient population of this size is of obvious importance. However, correctly investigating and managing the treatment for such patients can be challenging. On the one hand, a potentially serious, yet manageable condition must not be overlooked. On the other hand, excessive anxiety over a problem that may not exist or may not be serious must not be created. Therefore, the finding of a normal angiogram in a patient with chronic chest pain in whom coronary disease was suspected prior to the procedure must lead to a thorough investigation (Figure 1). The pathophysiologic features, investigation, and treatment of chest pain in these patients are the subject of this review.

ARE THE CORONARY ANGIOGRAMS TRULY NORMAL?

In an important minority of patients, definite coronary abnormalities may account for the presence of angina pectoris and myocardial ischemia in spite of what may have been interpreted initially as a normal coronary angiogram. Possibilities include large-vessel coronary vasospasm, missed coronary artery lesions, congenital coronary anomalies, and myocardial bridges.

Large-Vessel Coronary Vasospasm

There seems to be less interest today in large-vessel coronary vasospasm than there was in the 1960s and early 1970s. The reason for this may be a true decrease in prevalence as a result of more attention to coronary risk factors or the more liberal use of calcium channel blockers. It is also possible, however, that cases are going undetected. Angina due to vasospasm often occurs at rest, and good exercise tolerance is maintained. Thus, the history differs from that of classic Heberden angina and may be dismissed as not “organic.”

Ergonovine testing was very popular in the late 1970s and early 1980s, but today it is rarely performed. It has proven to be very useful in the diagnosis and care of patients with possible spasm and has enhanced our knowledge of the pathophysiologic mechanisms of myocardial ischemia. Two large series established the safety and utility of the test. Bertrand et al performed it on a wide spectrum of patients including a large subset with fixed coronary disease and did not encounter serious complications. The series by Harding et al included more than 3000 patients with normal or near normal coronary angiograms; complications occurred in only 11 patients (0.37%) and there were no deaths. A positive test result requires findings of a segmental reversible narrowing of at least a 75% diameter stenosis and chest pain. An example of angiographically documented spasm induced by the administration of 0.25 mg of intravenous ergonovine maleate is...
shown in Figure 2. In controls, up to an 18% diffuse diameter reduction can occur without ST-segment shift or chest pain. If there is no chest pain, one is less certain about the diagnosis. Conversely, chest pain without angiographic coronary spasm does not constitute a positive test result. Patients with esophageal disease can experience chest pain with the administration of intravenous ergonovine. With these criteria for a positive test result (ie, chest pain and angiographic spasm) ergonovine provocation has excellent predictive accuracy for the diagnosis of coronary spasm with a sensitivity of 91% to 100% and a specificity of 93% to 96%. It is safe and inexpensive, and in patients with possible coronary vasospasm, it is important to establish the diagnosis for at least 2 reasons. First, coronary vasospasm is a common cause of sudden death in patients with structurally normal hearts, and the risk can be reduced with appropriate calcium channel blocker therapy. Second, there are therapeutic implications. β-Blockers may be ineffective and possibly even detrimental in patients with vasospasm, presumably by unmasking α-adrenergic vasoconstriction. Calcium channel blocking drugs are the pharmacological approach of choice, and in patients with refractory vasospasm, more so than in patients with fixed coronary disease, therapy with a combination of calcium channel blocking drugs (for example, diltiazem and nifedipine) may be effective when a single agent has failed.

Missed Coronary Artery Lesions

The introduction of selective coronary angiography by Sones and Shirey represents one of the major advances in the management of ischemic heart disease. Angiographic findings have been consistent and reliable in predicting mortality. Relatively modest angiographic progression is a strong independent predictor of coronary events. Coronary angiography permits a safe, rapid, and cost-effective method of visualizing the entire large and medium vessel coronary tree.

However, coronary angiography has limitations and pitfalls. Angiographic autopsy discrepancies were the subject of studies in the early 1970s. Later, Glagov et al clarified that one of the mechanisms for the discrepancy was because compensatory enlargement of atherosclerotic coronary arteries may keep pace with plaque growth and maintain vessel lumen. Over the last 20 years, intravascular ultrasound (IVUS) and more critically reviewed angiography have permitted the identification of certain troublesome angiographic lesions and patterns that may lead to the erroneous conclusion that an angiogram is normal. These include the following:

Diffuse Disease. Diffuse disease can reduce coronary flow reserve and cause angina; yet the lumen can remain constant, be apparently preserved, and be misinterpreted as an inherently small lumen artery. Nissen and colleagues found that two...
thrits of angiographically normal segments were abnormal on IVUS, and one third of these showed diffuse concentric disease. Diffuse disease should be suspected when reviewing an angiogram if there is any irregularity or if the ongoing branches are larger in diameter than the proximal arteries. Figure 3 shows a smooth left main coronary artery, which, however, is of smaller diameter than either of its branches, and IVUS confirmed diffuse left main stem disease.

Eccentric Plaques. Intravascular ultrasound studies have also shown that eccentric plaques may go undetected in angiographic studies. Such lesions may only lighten the contrast column without apparent diameter reduction if the slit is viewed in its widest diameter.

Flush Occlusions. Flush occlusions may go undetected unless all segments of the myocardium are reviewed for matching blood supply. They may also be missed if longer cinecoronary angiography runs have not been performed to permit sufficient time for distal segments to opacify in a retrograde fashion by collaterals.

Vessel Foreshortening. It may be difficult to visualize some foreshortened segments, which are sometimes surprisingly long. When such segments are identified they can usually be “unforeshortened” with unconventional oblique angulations or continuous rotational views.

Aorto-ostial Lesions. Aorto-ostial lesions can exist alone and can represent aortic rather than coronary disease. The tendency to use smaller French-size diagnostic catheters may result in their passage through and beyond an ostial lesion with failure to opacify the diseased segment. When in doubt, sinus flushes should be performed.

Branch Ostial Lesions. Branch ostial lesions can be difficult to detect and may represent a challenge to identify. Atherosclerosis has a propensity for bifurcation locations, possibly because of high shear stress. Right coronary artery branches at the crux and proximal left anterior descending (LAD) branches are notoriously difficult to visualize and ostial lesions of these branches may be overlooked.

Overlapping Side Branches. Overlapping side branches on occasion may obscure a field of interest, and multiple oblique views may be required. Figure 4 illustrates such a case.

Disease of the Left Main Coronary Artery. Disease of the left main coronary artery can be underestimated or go totally undetected. The greatest discrepancy between angiographic findings and pathologic features occurs in left main stem disease. The study by Glagov et al was based on an examination of the left main coronary artery. On average, it is less than 1 cm long, arises slightly posteriorly, and the true ostium can be identified only in a left anterior oblique view. It then courses anteriorly and inferiorly and is least foreshortened in a straight or slightly angulated anteroposterior view. A combination of these views may be required to exclude disease.

When the angiograms have been read as normal and yet the clinician suspects (based on a classic history or documented ischemia) that a significant stenosis may have gone undetected, then further investigation should be considered. The potential usefulness of IVUS imaging is shown in Figure 5. Coronary angiography in this case was performed because of unstable angina and continued rest pain. On first examination, the angiogram was read as normal. However, on review there were 3 contentious areas that were clarified with IVUS imaging, and the final diagnosis was moderate coronary atherosclerosis, possibly with superimposed coronary spasm. Physiological assessment of borderline or angiographically obscure lesions or segments can also be performed using Doppler flow or pressure wires and pharmacological coronary arteriolar vasodilation (usually with the administration of intracoronary adenosine) to measure coronary flow reserve. This has proven to be reliable in longitudinal studies in which coronary angioplasty was performed or

Figure 3. A. Left coronary angiogram in a 30° right anterior oblique, 30° cranial projection demonstrating a diffusely narrowed left main coronary artery (arrow) with a diameter smaller than either the left anterior descending artery or the circumflex artery. B. Intravascular ultrasound image of the left main coronary artery (arrow) demonstrating a 61% area stenosis (2.9F, 30-MHz Ultracross Catheter, Boston Scientific Corporation, Boston, Mass). Reproduced with the permission of Canadian Journal of Cardiology (1999;15:297-302).
withheld based on flow reserve measurements.

It is important clinically to detect mild to moderate atherosclerotic lesions on a coronary angiogram for at least 2 reasons. First, it has been clearly shown that it is often the mild or moderate lesions that are the most vulnerable to plaque rupture and account for up to two thirds of the cases of acute coronary syndromes. The milder lesions are often softer, lipid-rich plaques and more prone to disruption. Angiography cannot predict future sites of coronary occlusion, but a recent study suggested that IVUS may have this potential. The results of an initial baseline IVUS and angiogram with a second angiogram triggered by a clinical event showed that large eccentric plaques with echolucent zones had an increased risk of producing a subsequent acute coronary event even though the lumen was intact at the initial study. Second, serial angiographic follow-up studies in patients with completely normal coronary arteries indicate that new development of atherosclerosis over a 4- to 5-year period is very unusual, whereas patients with mild coronary atherosclerosis usually show a rate of disease progression that is not notably different from that of patients with significant coronary artery disease.

Congenital Coronary Anomalies

There are other instances where the findings of an angiographic study may be incorrectly read as normal. Congenital anomalies of the coronary arteries may be overlooked and certain variations may result in ischemia in the absence of coronary atherosclerosis. The importance of their detection is also underlined by their association with sudden death that often occurs in younger people.32 The most important anomaly for this review is the origin of the circumflex artery arising from the right coronary artery or right sinus of Valsalva. Its relevance relates to 3 factors: first, it is the most frequent anomaly, with a prevalence in angiographic findings of 0.45%; second, it is the only one in which the anomalous vessel is associated with a greater frequency of disease than is the case for nonanomalous arteries; third, it can easily go undetected if one mistakes an intermediate branch or a diagonal branch for the

Figure 4. A, Left coronary angiogram in a 50° left anterior oblique, 30° cranial projection (arrow). B, Left coronary angiogram in a 30° right anterior oblique, 30° caudal projection (arrow). C, Localized left anterior descending artery stenosis (arrows; inset, magnified section) is shown in a 30° right anterior oblique, 80° caudal projection. The lesion is located just beyond the origin of a septal perforator that hides the lesions in other views (A and B).

Figure 5. Left coronary angiogram in a 60° left anterior oblique, 30° caudal projection and the intravascular ultrasound images of 3 segments. A, Ultrasound image of the mid–left anterior descending artery just beyond the origin of the diagonal branch (arrow) showing an eccentric plaque with a 47% area and 27% diameter stenosis. B, Ultrasound image of the proximal left anterior descending artery (arrow) showing a fibrous eccentric plaque with a 51% diameter and 30% area stenosis. The angiogram shows a lighter dye column in this segment. C, Origin of the diagonal branch with an apparent angiographic narrowing (arrow) but patent on intravascular ultrasound imaging (3.2F, 30-MHz, Ultracross Catheter, Boston Scientific Corporation, Boston, Mass).
circumflex artery or assumes that it is congenitally absent. Other anomalies are less frequent and less likely to be missed; however, they may be associated with myocardial ischemia in the absence of atherosclerotic narrowing. These include the left coronary artery arising from the right sinus of Valsalva or the right coronary artery proper and the right coronary artery arising from the left sinus of Valsalva.33 Congenital large coronary arteriovenous or cardiopulmonary fistulae are usually obvious, but subtle ones can be missed as can arteriocameral fistula connecting coronary arteries with cardiac chambers.34 They may cause ischemia by a “steal” phenomenon and are suggested when there is rapid opacification of the left ventricular chamber during coronary angiography.

**Myocardial Bridges**

Finally, patients with myocardial bridges but with otherwise normal coronary angiograms may have angina. These bridges consist of segments of the LAD artery that course from their subepicardial surface location into the myocardial tissue and then back out. Transient systolic constriction occurs, which resolves during diastole. The overall incidence at coronary angiography is approximately 1%. Chest pain is frequent, and there is electrocardiographic and metabolic evidence that if there is greater than a 75% diameter systolic compression, ischemia may occur during tachycardia.35 Flow reduction may even extend into diastole if the compression is severe. Surgical decompression is effective treatment,37 and more recently, stent implantation in 3 patients with persistent and severe angina normalized hemodynamic abnormalities and coronary flow reserve and resulted in clinical improvement.38

**IS THERE A NONCORONARY CARDIAC CAUSE OF ISCHEMIC CHEST PAIN?**

Several cardiovascular diseases can contribute to or cause myocardial ischemia in the absence of coronary disease. The most important are valvular heart disease, cardiomyopathy, and hypertension. Valvular heart disease, particularly aortic stenosis and aortic regurgitation, is associated with impaired coronary flow reserve and increased myocardial oxygen requirements, and angina is a frequent presenting symptom. Angina may occur with all forms of cardiomyopathy but most frequently occurs in the hypertrophic syndromes in which myocardial oxygen supply balance is particularly tenuous.30 The importance of this syndrome for this review is that, clinically, the diagnosis is often missed. The diagnosis is made on the basis of the echocardiogram, but if the disease is not suspected, echocardiography may not be performed. Chest pain is also a frequent complaint in patients with dilated cardiomyopathy, and it is usually ischemic in origin.31 The most frequent entity associated with chest pain and normal coronary angiograms is hypertension. In one study of 41 patients with hypertension and normal coronary angiograms, 15 (37%) of the 41 patients had chest pain.42 The suggested mechanisms included increased left ventricular mass, medial arterial hypertrophy,43 diastolic dysfunction, and impaired coronary vasodilation.44

**IS THERE A NONCARDIAC CAUSE OF CHEST PAIN?**

Almost any condition can mimic angina pectoris. Pain characteristics may be helpful in excluding other syndromes. However, even after a careful history, 2 areas remain diagnostic challenges: the distal esophagus and the musculoskeletal system.

**The Distal Esophagus**

There are several reasons why esophageal pain may be mistaken for cardiac pain. The distal esophagus and the heart share a common afferent nerve supply; hence, pain location and radiation may be identical.45 Certain types of exertion, particularly those that increase intra-abdominal pressure, may precipitate esophageal pain. Therapy with nitroglycerine may relieve esophageal spasm. The reproduction of chest pain with intravenous ergonovine, which was thought to be pathognomonic of coronary spasm, has now been shown to occur with esophageal motor disorders.41 In addition, patients with documented coronary artery spasm often have esophageal spasm as well, suggesting a unifying mechanism, and both can be provoked by hyperventilation.46 Cardiac and esophageal disease also share risk factors such as obesity and smoking. Acid reflux may reduce the angina threshold in patients with established coronary disease.47

The causes of esophageal pain are reflux esophagitis, esophageal motility disorders consisting of high-amplitude, long-duration contractions (also called spasm), and hernia incarceration. The classic esophageal pain syndrome is easily identifiable: it is felt as a heartburn moving toward the pharynx, sometimes accompanied by pharyngeal burning and dysphagia, and it is aggravated by the supine position, particularly nocturnally. The diagnosis can be confirmed with a barium swallow and endoscopy. In more difficult cases, manometry, acid perfusion studies, ambulatory 24-hour pH monitoring, and provocative tests may be necessary. If the patient’s typical pain syndrome can be reproduced with the administration of either intravenous ergonovine or intravenous methacholine chloride, with simultaneous abnormalities in manometric measurements such as high-amplitude and long-duration contractions, or with acid perfusion of 0.1-M hydrochloric acid into the midesophagus, then the diagnosis of an esophageal rather than cardiac disorder is fairly certain.

**Chest Pain of Musculoskeletal Origin**

The thoracic compartment is a complex structure consisting of 24 ribs, 12 vertebrae, 12 chondrosternal joints, 14 costochondral joints (these 26, all synchondroses), in total 38 costovertebral and costotransverse joints (all synovial lined), 2 sternoclavicular joints, 1 manubriosternal joint, and 1 xiphisternal joint as well as intercostal muscles, ligaments, tendons, and a complex nerve supply. In a consecutive series of patients presenting to cardiologists with suggestive cardiac pain, 10% had a costosternal syndrome.48

Given the elaborate anatomy described above, perhaps it is sur-
prising that chest wall pain is not even more common. Chest wall pain differs from other causes of chest pain by the presence of findings on musculoskeletal examination and physical examination and provocation of the pain by simple maneuvers whereby the diagnosis can often be made at the bedside without the need for further testing. On occasion, ancillary investigations such as rib radiography and cervical and thoracic spine radiography, computed tomography, and magnetic resonance imaging may be helpful.

Pain arising from the shoulder and cervical and thoracic spine may be referred to the chest wall with the same nerve supply and may be associated with deep or myofascial tenderness. The C5-C6 and C6-C7 syndromes are not only associated with tenderness on palpation of the anterolateral corners of the bordering vertebrae, but also with points of referred tenderness over the anterior chest. Costochondritis is a self-limited inflammatory disorder of unknown etiology that may recur. Because it most often affects the upper costal cartilages, it is often mistaken for cardiac disease. Diffuse tenderness invariably occurs over the involved costochondral or costosternal joints without swelling, and the pain can usually be reproduced by palpation of the chest wall.

The fibrositis syndrome (or fibromyalgia or the myofascial syndrome) is a poorly understood disorder that occurs much more frequently in women than in men and is a common cause of chest wall pain. There is no objective evidence of inflammation, and there is unrestricted movement of joints. It is characterized by tender “trigger” points that may cause pain at a distant site. Although chest pain in this syndrome often occurs with exertion, it is almost always with the use of the arms rather than the legs, in contrast to angina in which the opposite is true.

CHEST PAIN WITH A BROAD SPECTRUM OF POSTULATED MECHANISMS: SYNDROME X

The term syndrome X arose from a publication by Arbogast and Bourassa in 1973. They described 10 patients (whom they called group X) who had normal coronary angiograms but had chest pain typical of angina. They compared these patients to 11 patients with coronary disease and angina. The response to rapid atrial pacing of the patients with syndrome X was normal with increased cardiac index, decreased left ventricular end diastolic pressure, and an improved ventricular function, in contrast to the patients with coronary disease whose ventricular function deteriorated. Both groups behaved similarly metabolically, either decreasing lactate extraction or frankly producing lactate. In spite of this, a diagnosis of true ischemia was questioned by the authors and has been questioned since by others who have shown, in contrast to the study of Arbogast and Bourassa, a nonischemic pattern of myocardial substrate uptake and utilization both at rest and in response to pacing. Follow-up observations of these patients suggested a benign condition compared with other syndromes causing ischemia.

More than 20 years after the initial publication, little more definitive information is known about patients with this syndrome. Many theories of cardiac syndrome X have evolved through the years, some of which will be reviewed here. One theory will not apply to all patients, and the theories overlap. Much is speculative because this entity seems to defy scientific testing.

Impaired Coronary Flow Reserve

Early on, it was postulated that coronary flow reserve was impaired in syndrome X, and in the absence of large-vessel disease, it was thought that the abnormality resided at an arteriolar level. Normally, coronary flow increases by severalfold with exercise, and this can be measured invasively with Doppler velocity flow wires or noninvasively with positron emission tomography. In a series of well-selected patients with syndrome X, the coronary flow reserve ratio was 2.72 ± 1.39 vs 5.22 ± 1.26 in “controls” (ie, patients with transplants) (P < .01). In this study, 40 of the 53 patients with syndrome X had a flow reserve of less than 3.5, while this was true of only 1 of 20 controls. A lower than normal resting microvascular tone may also contribute to impaired reserve by allowing little room for further vasodilation. Using positron emission tomography and intravenous dipyridamole in 17 patients, Geltman et al found that in 8 of them, coronary flow reserve was normal, but in the other 9, resting flow was higher and maximal flow was lower than normal, thus reducing coronary flow reserve. Thus, modulation of microvascular tone may be disturbed in some patients with this syndrome.

Microvascular Spasm

The problem at the level of the resistance arterioles may be microvascular spasm. Hackett et al were able to provoke typical angina with the administration of intracoronary ergonovine in 5 patients who had normal coronary angiograms, suggesting that they had ergonovine-induced and, presumably, spontaneous microvascular spasm. Egashira and colleagues found that the mean increase in acetylcholine-induced coronary flow was lower in 9 patients with syndrome X than in 10 controls in spite of comparable large-vessel dilation with the administration of acetylcholine. Thus, impaired nitric oxide release at a microvascular level might induce vasospasm in these patients, although vascular hyperreactivity is another possible mechanism.

Patchy Prearteriolar Vasoconstriction

A theory developed by Maseri and colleagues suggests that the problem may be located in the prearteriolar vessels. These authors postulated that there is patchy constriction of prearteriolar vessels resulting in downstream release of adenosine. Local adenosine accumulation might stimulate afferent cardiac nerves and produce anginalike chest pain without any true ischemia. Aminophylline is an antagonist of adenosine P1 receptors, and in one double-blind crossover study, pretreatment with aminophylline was effective in reducing ischemia and chest pain and extending exercise test duration in patients with syndrome X.
Disease of the Small Arteries

Small arteries account for 40% of coronary vascular resistance, with the remainder at the arteriolar level. In some patients, pathological disease of small arteries may be an explanation for syndrome X, but these vessels are too small for the measurement capability of angiography, which is generally considered to be 0.5 mm or larger. They can be assessed indirectly by observing and measuring the speed of dye flow.

Slow dye flow with normal epicardial arteries has been observed in separate series of patients with syndrome X. In one report, 10 of 143 patients with syndrome X showed this slow dye flow, and results of left ventricular biopsies in all 10 showed small artery thickening and lumen reduction. Mosseri and colleagues described 16 cases of syndrome X, all of which demonstrated slow flow of the dye column. Right ventricular biopsy specimens from these patients showed evidence of intramural coronary artery fibromuscular hyperplasia and swollen capillaries and a relative lack of capillaries. Strauer performed endomyocardial biopsies on 220 patients with angina and normal coronary angiograms: 85 of the biopsy specimens showed evidence of small-artery vasculitis and a variety of collagen vascular diseases such as systemic immune complex vasculitis, scleroderma, and periarteritis, and the remaining 135 showed evidence of systemic hypertension and hypertensive hypertrophy of the small arteries. Therefore, a diligent search for systemic evidence of vasculitis or immune complex disease would be appropriate in normotensive patients with this syndrome.

Occult Large-Vessel Disease

Results of an IVUS study of 30 patients with syndrome X emphasize the heterogeneity of the syndrome. This study included performing resting IVUS imaging of all 3 coronary arteries and exercise IVUS imaging in the artery that showed the most abnormal resting IVUS finding. Three patterns evolved: (1) a normal IVUS finding (12 patients); (2) atheromatous plaque (10 patients); and (3) marked intimal thickening with no plaque (8 patients). The patients with a normal IVUS finding (pattern 1) showed coronary vasodilation with exercise, and the patients with plaque or intimal thickening (patterns 2 and 3) showed vasoconstriction with exercise. Thus, patients with syndrome X may have subtle large-vessel disease, which may account for their stress-induced angina.

Pain Due to Excessive Adenosine Effect Without Ischemia

There is growing proof that one mediator of cardiac pain is adenosine, which activates ventricular sympathetic afferents. Intracoronary adenosine administration causes chest pain in patients with typical angina. Aminophylline seems to have a dual action in the myocardial microvascular circulation: it blocks adenosine P2, pain receptors on afferent sympathetic nerve fibers but also competitively blocks dipyridamole-induced inhibition of cellular adenosine reuptake. Intravenous aminophylline is instantaneously effective in relieving the pain that may occur with dipyridamole perfusion testing. This suggests that the fault for some patients might be an aberration of adenosine metabolism resulting in adenosine accumulation in the absence of ischemia.

Psychological Disorders

Psychosocial problems are common in patients with noncardiac chest pain. Wielgosz et al found a high incidence of hypochondriasis in patients with chest pain and normal coronary angiograms. Beitman et al reported a 34% incidence of panic disorders among patients with normal coronary angiograms. In a group of patients with chest pain who were referred for myocardial stress scintigraphy and had a negative scan result, 56% met the criteria for panic disorder. Finally, among 41 consecutive patients consulting the emergency department of a cardiology hospital with a chief complaint of chest pain, 25% met structured interview criteria for panic disorder. In these patients, simple reassurance may not be sufficient to relieve the patient’s anxiety, and referral to a mental health professional may be required.

Hormonal Deficiency

In contrast to the sex distribution of coronary heart disease, most patients with syndrome X (almost 80%) are women and most are hypoestrogenic. It has been postulated that this syndrome represents a generalized alteration of vasomotor control (including dysfunction of the coronary microvasculature) due to ovarian hormonal deficiency. In a double-blind, crossover, placebo-controlled trial, there was a significant reduction of chest pain episodes in these patients with the application of estradiol-17β patches for 8 weeks, although there was no change in exercise test duration.

Other Theories and Contributing Factors

Forty-one patients with chest pain and normal coronary arteriograms had platelet hyperaggregability in response to adenosine diphosphate or epinephrine stimulus, but the clinical relevance of this in vitro observation requires confirmation. Abnormal endothelial function has received increased attention of late, since at a large-vessel and arteriolar level, endothelial function is important in maintaining coronary flow reserve. Hyperlipidemia, aging, diabetes, smoking, and lack of physical exercise alters endothelial function and may contribute to ischemia and angina in the absence of angiographic coronary disease.

Therapeutic Implications

From all of this chaos, how can one develop an investigative and therapeutic management plan for a patient in whom this syndrome is suspected? Risk factor modification where indicated should be initiated. Normalizing lipid levels improves positron emission tomography perfusion abnormalities. Estrogen replacement may improve symptoms if the patient is a woman and is hypoestrogenic. Nicotine discontinuation may ameliorate symptoms. Exercise training enhances endothelial function.
L-arginine (a precursor of endothelial-derived nitric oxide) therapy and dietary supplementation represent a new approach to treating endothelial dysfunction and have been shown to improve endothelial-dependent vasodilation in patients with syndrome X and in patients with coronary disease. In a study by Lerman et al., L-arginine dietary supplementation for 6 months improved coronary small-vessel endothelial function and symptoms.

Nitrates may not only be ineffective but may even reduce coronary flow. One study showed that treadmill performance became worse with sublingual isosorbide dinitrate therapy in patients with syndrome X in contrast to improvement in patients with coronary disease. As discussed above, theophylline preparations have been used with some success, but before attempting a novel therapeutic approach such as this, one should be cognizant of the variable nature of the symptoms in this syndrome.

CONCLUSIONS

How does the clinician approach the treatment of a patient with normal coronary angiograms in whom angina and coronary disease were suspected prior to angiography? First, the angiograms should be reviewed critically for any possibly missed or undercalled lesions. If the history suggests vasospastic angina, ergonovine testing should be considered. If ischemia is documented on stress-induced myocardial scintigraphy and there is mild or moderate coronary disease or segments that are not well visualized, then a restudy with IVUS imaging or flow reserve measurements could be pursued. A cardiac echocardiogram is mandatory because it is an excellent screening tool for excluding other cardiac causes of angina. If symptoms suggest a non-cardiac cause of chest pain should be investigated, and finding the cause may be relatively easy as in the case of costochondral or costosternal syndromes or more labor intensive as in the case of esophageal motility disorders. Finally, many patients’ conditions will remain undiagnosed, and they will be labeled as having syndrome X, a heterogeneous chest pain syndrome often of undetermined etiology. In these patients, risk factors for coronary disease should be appropriately treated, which will improve vascular function. In general, antianginal medications should be avoided since they are usually ineffective and may, as in the case of nitrates, even worsen exercise intolerance and symptoms. Patients who show scintigraphic or echocardiographic signs of myocardial ischemia should be observed more closely and have their clinical status reevaluated whenever appropriate. However, the diagnostic label of coronary disease should be avoided. On the contrary, reassurance should be given because their risk of ever developing coronary disease is minimal. In fact, the long-term prognosis of patients with truly normal coronary angiograms and chest pain for whom other causes have been excluded is excellent and may even exceed that of the general population.

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