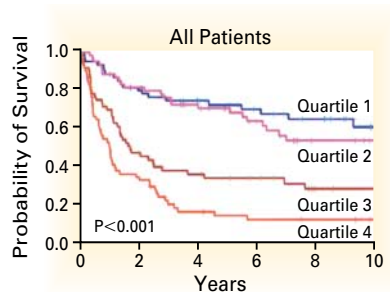




This Week in the Journal

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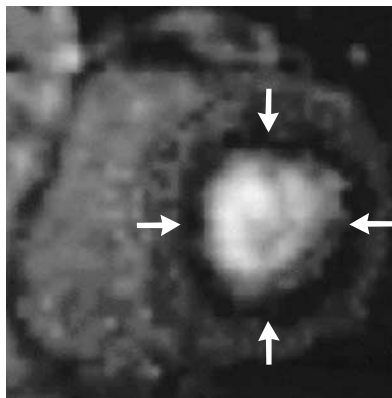


Use of Gene-Expression Profiles to Predict Survival after Chemotherapy for Diffuse Large-B-Cell Lymphoma

In a large group of diffuse large-B-cell lymphomas, DNA microarrays identified three patterns of gene expression that were correlated with the likelihood of survival after chemotherapy. Individual genes within these patterns formed molecular signatures that had an even stronger correlation with survival after chemotherapy. The predictive power of the molecular signatures was independent of the international prognostic index.

DNA microarrays reflect the activity of tens of thousands of genes in a sample of tissue. This study of the most common lymphoma in adults focused on more than 12,000 genes expressed by lymphoid tissue and found 17 that were strongly related to the outcome. This work is an example of how microarray technology is leading to clinically useful insights into the molecular genetics of cancer.

see page 1937 (editorial, page 1998)



Abnormal Subendocardial Perfusion in Cardiac Syndrome X

Patients with cardiac syndrome X have angina and abnormal exercise-test results but normal findings on coronary angiography. Although myocardial ischemia has been suspected to be the cause, this has been difficult to document. In this study, myocardial-perfusion magnetic resonance imaging demonstrated abnormal subendocardial perfusion during adenosine infusion in 20 patients with the syndrome.

Perfusion magnetic resonance imaging is a very sensitive technique for the detection of myocardial ischemia. The findings are important because they point clearly to ischemia as the cause of cardiac syndrome X and provide new insight into approaches to treatment.

see page 1948 (Perspective, page 1934)

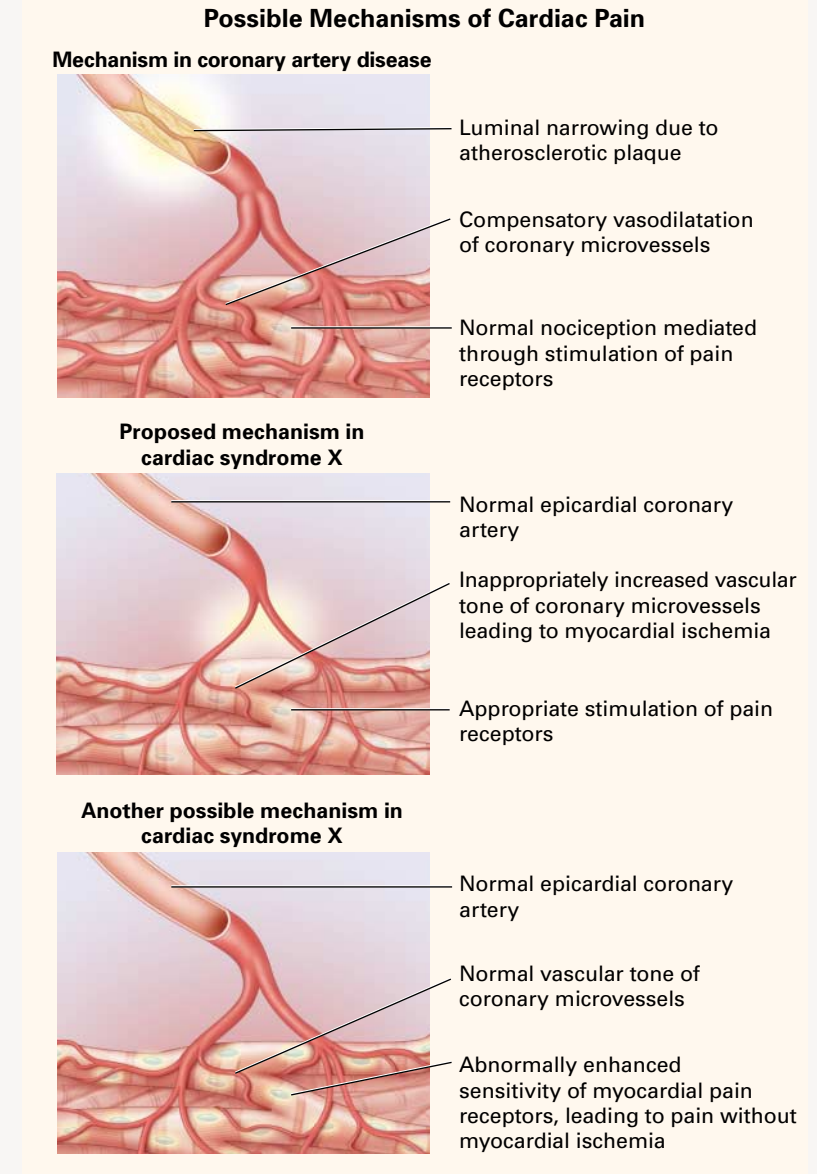
PERSPECTIVE

Myocardial Ischemia and the Pains of the Heart

Angina pectoris is usually caused by myocardial ischemia due to atherosclerotic narrowing of the epicardial coronary arteries, with or without local vasoconstriction or a superimposed thrombus, that limits the supply of blood to the myocardium. This leads to the stimulation of pain receptors that trigger the patient's perception of anginal symptoms (see Figure). Therefore, when a physician cares for a patient with chest pain whose coronary anatomy is unknown, the main question is whether the symptoms are due to coronary atherosclerosis. This question is relevant for two reasons. First, atherosclerotic heart disease is the chief cause of death in Western societies. Second, the patient's symptoms and prognosis may be improved with drugs or revascularization.

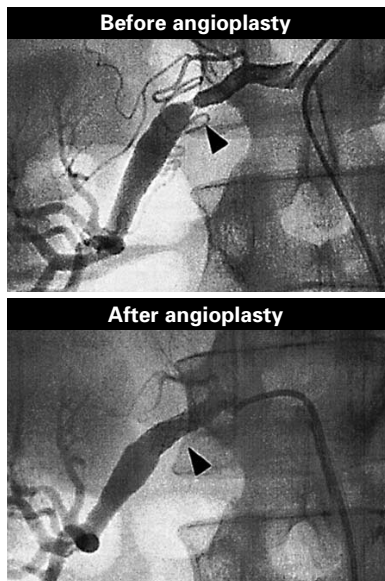
However, in up to 20 percent of patients with anginal chest pain, the coronary angiogram, usually obtained because of "positive" findings on one or more noninvasive tests, does not show clinically significant narrowing of the vessel lumen. In these cases, the physician must answer several important questions posed by the patient: Why do I have chest pain? Do I have heart disease? Can my condition be effectively treated, and if so, how? Will my problem worsen with time? Is my life expectancy shortened?

In this issue of the *Journal*, Panting et al. (see pages 1948–1953) attempt to answer the first two questions. The results of their study, performed with magnetic resonance imaging during infusion of adenosine, suggest that chest pain



in these patients is explained by ischemia secondary to diminished (or absent) vasodilatation of the coronary microvasculature, leading to relative underperfusion of the sub-endocardium (see Figure). On the basis of these findings, one would conclude that patients with chest pain, abnormal electrocardiographic changes during exercise, and normal coronary angiograms do indeed have a form of cardiac disease that accounts for their symptoms.

However, as the term used to describe this condition (cardiac syndrome X) conspicuously implies, the evidence that myocardial ischemia is the responsible mechanism is far from conclusive. Several previous studies of patients with cardiac syndrome X have appeared to demonstrate the presence of ischemia on the basis of abnormal results of various tests performed under conditions of stress. In turn, each study was found not to be re-



Endothelial Function and Oxidative Stress in Renovascular Hypertension

Renovascular hypertension activates the renin–angiotensin system, which can increase oxidative stress and vascular endothelial dysfunction. This study examined forearm blood flow as a marker of endothelial dysfunction before and after transluminal renal-artery angioplasty in 15 affected subjects and in 15 controls. The response of forearm blood flow to acetylcholine, an endothelium-dependent vasodilator, was diminished in subjects with renal-artery stenosis as compared with controls, and it improved after angioplasty. Responses to isosorbide dinitrate, an endothelium-independent vasodilator, were similar in all conditions in both groups. Indexes of oxidative stress such as urinary 8-hydroxy-2'-deoxyguanosine and serum malondialdehyde-modified low-density lipoprotein decreased after angioplasty.

These findings suggest that increased oxidative stress is involved in impaired endothelium-dependent vasodilatation in patients with renovascular hypertension.

see page 1954 (editorial, page 1999)

producibile. Even in the study by Panting et al., none of the patients with cardiac syndrome X had the perfusion defects consistent with myocardial ischemia on thallium scanning that were reported in previous studies. Studies with stress echocardiography consistently demonstrated that, despite the provocation of chest pain, patients had no impairment in contractility — usually an early phenomenon in the cascade of events that follow myocardial ischemia.

Although reasonable explanations for these discrepancies are provided, certain issues remain unresolved. For example, given that adenosine is a vasodilator that causes only small increases in myocardial oxygen demand, why would a lack of increase in perfusion, without any additional form of stress, lead to such severe ischemia and to the severe chest pain that the patients experienced? Is it possible that the images obtained represent true heterogeneity in transmural perfusion but not necessarily myocardial ischemia? Finally, stud-

ies demonstrating abnormal test results have been limited to a small number of patients, a fact that raises questions about the generalizability of the findings.

To complicate matters further, previous studies have shown that the typical chest pain reported by patients with normal coronary angiograms can be evoked by electrical stimulation of the right ventricle, which clearly does not cause myocardial ischemia. These and other studies that have used positron-emission tomographic scanning of the brain point toward an abnormally sensitive perception of cardiac pain in at least some of these patients (see Figure).

What about therapy and prognosis? Patients with normal coronary angiograms usually have a poor response to conventional antiischemic therapy, which may lead to the unnecessary performance of repeated coronary angiography over the years because of recurrence of chest pain. Blocking cardiac nociception with low doses of tricyclic antidepressants may alleviate the

symptoms. With regard to prognosis, studies have consistently shown that these patients have a life expectancy similar to that of the general population, with conduction abnormalities or mild left ventricular dysfunction developing in a minority of them during follow-up.

Thus, cardiac syndrome X (i.e., the presence of anginal chest pain despite angiographically normal coronary arteries) remains an enigma. The study by Panting et al. is important because, if confirmed by subsequent studies, it may make possible the accurate identification of patients who truly suffer from ischemia and who therefore require closer observation and more aggressive therapy. For the time being, most patients with chest pain and normal coronary angiograms need only appropriate risk-factor modification and reassurance that their symptoms are not caused by the same disease that kills millions of people every year.

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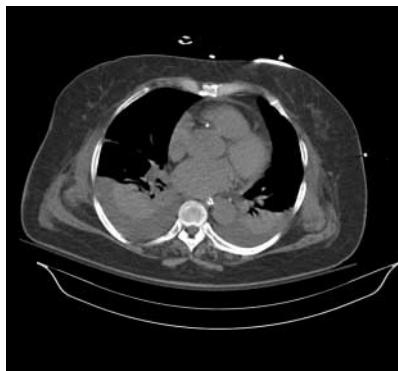
“During a median follow-up of 10 months there were only two relapses.”

Fumagillin Treatment of Intestinal Microsporidiosis

This double-blind trial involved 12 immunocompromised patients with chronic diarrhea and *Enterocytozoon bieneusi* infection. Treatment with fumagillin (60 mg per day orally for two weeks) led to some symptomatic improvement and to clearance of the parasite in six of six patients, as compared with none of six in the placebo group (P=0.002). All patients were eventually treated with fumagillin, but severe thrombocytopenia or neutropenia developed in three patients.

There has been no effective treatment for intestinal microsporidiosis, which is a cause of chronic diarrhea, malabsorption, and wasting in severely immunocompromised patients. Fumagillin, which was once used to treat malaria, is an effective treatment against this opportunistic parasitic infection.

see page 1963

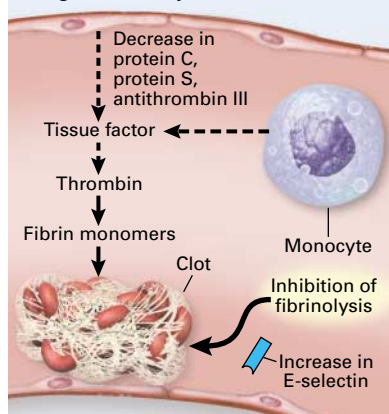


Clinical Practice: Pleural Effusion

A 70-year-old man with an 80-pack-year history of smoking and a history of congestive heart failure presents with increasing shortness of breath. He also has aching chest pain on the right side that worsens with deep inspiration. He is afebrile. The chest radiograph reveals asymmetrical bilateral pleural effusions, with more fluid on the right. How should this patient be evaluated?

see page 1971

Coagulation Response to Heat Stroke



Medical Progress: Heat Stroke

Knowledge of the molecular and cellular events in heat stroke has advanced steadily during the past decade. It is now known that heat stroke is associated with injury to multiple tissues and organs as a result not only of the cytotoxic effect of heat, but also of the inflammatory and coagulation responses of the patient. Altered expression of heat-shock proteins may also have a role in the pathogenesis of heat stroke. This article reviews current understanding of the pathophysiology of heat stroke and advances in therapy.

see page 1978