Unstable angina is a clinical syndrome, analogous to hypertension; it is not a specific disease, such as pneumococcal pneumonia. Unstable angina is commonly classified by use of simple clinical descriptors, such as the presence or absence of ischemic chest discomfort at rest, as well as ECG changes and biochemical markers of myocardial injury during and after ischemic episodes. Although these clinical descriptors are helpful in estimating prognosis and are used widely in determining the intensity of treatment, they provide little information regarding the cause of the syndrome.

The management of any illness is improved immensely by the elucidation of its cause. For example, in patients with hypertension, identification of a specific pathogenesis, such as renovascular hypertension or mineralocorticoid-induced hypertension, allows for much more effective management than treatment based simply on the existence of hypertension of ill-defined cause. In unstable angina, it appears to be possible to distinguish 5 different, although not mutually exclusive, causes. These are summarized in the Table and are shown in Figure 1, an elaboration of a schema that was described previously.

Nonocclusive Thrombus on Preexisting Plaques

Unstable angina results from an imbalance between myocardial oxygen supply and demand. Probably the most common cause is reduced myocardial perfusion resulting from a nonocclusive thrombus on a fissured or eroded atherosclerotic plaque that often had caused only mild to moderate obstruction previously. Nonocclusive thrombi in patients with unstable angina have been demonstrated by coronary angioscopy and arteriography. They occur most commonly on complex, irregular lesions. Plaques that have undergone disruption often have a core that is rich in cholesteryl esters and tissue factor. They have a thin fibrous cap; disruption is caused by shear forces acting on the shoulder of the plaque. In patients with unstable angina, products of aggregating platelets are released into the coronary circulation, and there appears to be continued thrombus formation, often for months, after the index event. Nonocclusive coronary thrombi often become organized and incorporated into the growing plaque.

Treatment with antithrombotic agents (unfractionated heparin and low-molecular-weight heparin) and antiplatelet agents (aspirin, ticlopidine, and glycoprotein IIb/IIIa inhibitors) is beneficial in this form of angina. Perhaps tissue factor inhibitors will prove useful as well.

Dynamic Obstruction

A second form of unstable angina is caused by dynamic obstruction, ie, coronary vasoconstriction. Four subgroups are recognized. (1) The first is Prinzmetal’s variant angina, with intense focal spasm of a segment of an epicardial coronary artery not involved by coronary atherosclerosis. (2) In the second, also called Prinzmetal’s angina, the spasm occurs adjacent to a nonobstructive atheromatous plaque. Both of these forms of vasospastic angina appear to be due to hypercontractility of vascular smooth muscle and endothelial dysfunction occurring in the region of spasm. They are characterized by ST-segment elevation accompanying rest pain and can often be provoked by stimuli such as ergonovine, acetylcholine, or hyperventilation. Rarely, vasospastic angina is caused by allergic reactions, with mediators such as histamine or leukotrienes acting on coronary vascular smooth muscle. (3) The third subgroup results from nonfocal constriction of major coronary arteries containing atherosclerotic plaques. Such coronary vasoconstriction may be caused by adrenergic stimuli, cold immersion, or cocaine. Most commonly, coronary vasoconstriction may also occur when shear stress and/or humoral stimuli such as thrombin and substances released from platelets, including serotonin and thromboxane A2, act on dysfunctional coronary endothelium, with reduced production of relaxing factors and increased release of endothelin, causing contraction of coronary vascular smooth muscle. (4) The fourth is microcirculatory angina. In this condition, the ischemia is secondary to constriction of the small intramural coronary resistance vessels, which in some instances is also caused by endothelial dysfunction. The epicardial coronary arteries appear normal on coronary arteriography, but the clearance of contrast material from the myocardium may be prolonged.

Dynamic obstruction often responds to coronary vasodilators: nitrates and calcium antagonists.

Progressive Mechanical Obstruction

The third form of unstable angina results from severe, organic luminal narrowing; perhaps its “purest” form is the restenosis after percutaneous transluminal coronary angioplasty and other forms of catheter-based revascularization. However,
serial angiographic studies in many patients without previous intracoronary procedures have shown progressive luminal narrowing of the culprit vessel in the period just preceding the onset of unstable angina. In such cases, progressive coronary obstruction causes the severe imbalance between myocardial oxygen supply and demand that is responsible for this form of unstable angina.

Treatment of this cause of unstable angina consists of transcatheter or surgical revascularization. The benefit of mechanical revascularization is directly proportional to the contribution of the organic obstruction to the ischemia.

Inflammation and/or Infection
There is increasing evidence that arterial inflammation plays a role in atherogenesis and is responsible for thrombogenesis in some patients with unstable angina and other acute coronary syndromes. There may be an increase of circulating activated lymphocytes, as well as of neutrophil and monocyte adhesion molecules. Macrophages and T lymphocytes are present at the shoulder of atherosclerotic plaques. These cells may increase the expression of metalloproteinases and other enzymes that cause thinning of the fibrous cap, thereby predisposing to plaque rupture. Mononuclear cells exhibit enhanced secretion of cytokines, such as tumor necrosis factor (TNF-α) and γ-interferon. Elevations of acute-phase reactants, such as C-reactive protein and serum amyloid A, portend a poor prognosis in patients with unstable angina. These cells may increase the expression of metalloproteinases and other enzymes that cause thinning of the fibrous cap, thereby predisposing to plaque rupture. Mononuclear cells exhibit enhanced secretion of cytokines, such as tumor necrosis factor (TNF-α) and γ-interferon. Elevations of acute-phase reactants, such as C-reactive protein and serum amyloid A, portend a poor prognosis in patients with unstable angina.

Taken together, these observations suggest that inflammation may precipitate unstable angina. There is serological evidence that infection with organisms such as *Chlamydia pneumoniae*, virulent strains of *Helicobacter pylori*, herpes simplex virus, and cytomegalovirus are common in patients with chronic atherosclerosis and acute coronary syndromes; *C. pneumoniae* has been repeatedly identified in atherosclerotic plaques. It has been postulated that these organisms induce the production of cytokines, such as TNF-α and several interleukins, which may unfavorably alter local lipid metabolism, destabilize coronary plaques, stimulate platelet activation, and enhance thrombus formation.

The ability to recognize an inflammatory or infectious origin of unstable angina is still primitive, but the inflammatory markers C-reactive protein and serum amyloid A, as well as antibodies to *C. pneumoniae*, are becoming more widely available. These might form the basis for the management of patients with unstable angina in whom inflammation and/or infection plays an important role. It has been suggested that the increased leukocyte adhesiveness observed in some patients with unstable angina identifies those who will benefit from treatment with anti-inflammatory agents.

Two small studies suggest that macrolide antibiotics reduce the incidence of recurrent events in patients with unstable angina and acute myocardial infarction. Anti-inflammatory drugs,
In most cases, the cause of secondary unstable angina can be recognized and corrected. β-Adrenergic receptor blockers are often effective in reducing excess myocardial oxygen demands.

**Multiple Causes**

Figure 2A represents the most common form of unstable angina, in which an atherosclerotic plaque causing 60% luminal stenosis forms the background for a very severe obstruction (90% luminal stenosis) caused by a superimposed thrombus. Figure 2B represents severe epicardial spasm occurring adjacent to a mild obstruction. Figure 3A represents the situation in a patient with stable angina due to moderately severe atherosclerotic obstruction in whom unstable angina is precipitated by a rise in myocardial oxygen demand during an intercurrent illness. In many patients with unstable angina, several causes are responsible; Figure 3B illustrates the situation in which a moderately severe atherosclerotic obstruction is complicated by local inflammation and thrombus formation.

**Conclusions**

The therapy of most illnesses is more successful when it is not empirical but rather is directed against a clearly defined etiology. It is therefore important to define more clearly the various established causes of unstable angina enumerated above and to seek additional causes. An assessment of the contributions of the various causes to the clinical syndrome should lead to therapy that is tailored to the individual patient. This approach to unstable angina is likely to be rewarded not only by more effective control of the acute syndrome but also by the prevention of recurrent events.

**Secondary Unstable Angina**

This form of unstable angina is precipitated by conditions that are extrinsic to the coronary vascular bed. It can be caused by conditions that increase myocardial oxygen demand and those that impair oxygen supply, occurring against the background of coronary stenosis and chronic stable angina. Increases in myocardial oxygen demand may result from tachycardia, fever, thyrotoxicosis, endogenous and exogenous hyperadrenergic states, and elevations of left ventricular afterload—systemic hypertension and various forms of aortic stenosis. Unstable angina secondary to impaired oxygen delivery can result from anemia, hypoxemia, and hyperviscosity states. Hypotension can reduce coronary perfusion pressure and impair myocardial perfusion distal to an atherosclerotic obstruction, thereby causing severe ischemia.

**References**


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