UNDERSTANDING the pathophysiology of unstable angina has been a major research effort for over two decades. Over the years our understanding of this syndrome has changed as different causes for the syndrome were identified. Initially, it was thought that increased myocardial oxygen demand was responsible for rest ischemia in patients with unstable angina. Later, it seemed that decreased supply caused by coronary vasospasm may have been responsible for the symptoms in these patients. More recently, by pathologic, angiographic, and angioscopic studies, we find that atherosclerotic plaque disruption with thrombus formation is the primary cause of this and other acute syndromes. In this paper, I hope to present a clear understanding of the pathophysiology of unstable angina.

Definition of Unstable Angina

Unstable angina is a descriptive term for a spectrum of acute coronary syndromes lying somewhere between stable angina and myocardial infarction. Unstable angina is a complex condition that has also been described as preinfarction angina, crescendo angina, status anginosus, acute coronary insufficiency, and the intermediate coronary syndrome. These terms encompass the heterogeneity of the syndrome thereby making identification of a unified pathophysiology a difficult task. In diagnosing unstable angina either crescendo or new onset angina must be present.

Crescendo angina is defined as a more severe, prolonged, or more frequent pattern of an already existing stable angina. New onset angina occurs within one or two months of evaluation and on minimal exertion or at rest. In both situations there has been an abrupt increase or onset of symptoms. Electrocardiographic changes indicative of transient myocardial ischemia without serum enzymatic evidence of myocardial necrosis (elevation of creatine kinase > 2 times normal) should also be present to exclude some noncardiac causes of chest pain or discomfort. Braunwald has recently proposed an extensive classification system of unstable angina. The patients are subdivided on the basis of severity of symptoms, associated clinical circumstances, amount of antianginal medication, and the presence or absence of electrocardiographic changes with pain.

Pathophysiology of Unstable Angina

It is, at first, difficult to identify a unifying pathophysiologic mechanism for the development of unstable angina given the heterogenous nature of this clinical syndrome. We can safely state that myocardial ischemia in unstable angina is caused by a disruption in the balance between myocardial oxygen supply and demand. There are four possible mechanisms to be considered as possible causes of unstable angina: (1) progression of coronary artery disease, (2) vasospasm, (3) an increase in myocardial oxygen demand, and (4) a combination of any of the above. Recent data suggest that progression of coronary disease with the formation of an "acute lesion" represents the primary pathophysiology of unstable angina, as defined in the second paragraph, while vasospasm and increases in myocardial oxygen demand are mechanisms of ischemia in this syndrome.
Progression of Coronary Artery Disease

As mentioned above, recent evidence from angiographic, angioscopic, and pathologic studies suggest that the predominant pathophysiologic mechanism of unstable angina is atherosclerotic plaque disruption with superimposed thrombus formation leading to the progression of coronary disease. There are several factors that play key roles in both the disruption of an atherosclerotic plaque and subsequent thrombosis. These were identified by the following studies.

Angiographic Studies

Investigators have provided important insights into the pathophysiology of the syndrome of unstable angina through angiographic studies. It has been shown that unstable angina cannot be differentiated from stable angina by the quantitative analysis of coronary lesions. Both the extent and location of coronary atherosclerosis were similar for patients with unstable and stable angina pectoris. The only exception was the higher incidence of left main coronary artery stenoses seen in some of the patients with unstable angina. Progression of coronary artery disease was seen in approximately 75% of these patients who previously had stable angina and who now presented with unstable angina. In patients with continuing stable angina, only 33% showed progression of coronary artery disease.4,5 From these data it is apparent that the development of unstable angina is preceded by a progression of coronary atherosclerosis and maturation of a new "culprit" lesion.

Analysis of the qualitative appearance of coronary lesions has helped investigators differentiate arteriographic findings. The presence or absence of filling defects in the coronary artery is suggestive of intracoronary thrombus. The incidence of these filling defects has varied widely between studies (6% to 85%).6-9 This is probably due to differences in the study design of these trials and to differences in the definition of an intracoronary thrombus.

Qualitative analysis of coronary angiograms also supplies critical information regarding the role of plaque rupture and thrombosis as the pathophysiologic mechanism in unstable angina. In a study by Ambrose et al,10 the angiograms of over one hundred patients with either stable or unstable angina were qualitatively assessed. Coronary lesions were categorized according to their angiographic morphology based upon the findings of a postmortem angiographic study of Levin and Fallon.11 Significant coronary obstructions (> 50% diameter stenosis) were categorized into one of the following morphologic groups: concentric (symmetric narrowing); type I eccentric (asymmetric with smooth borders and/or a broad neck); type II eccentric (asymmetric with a narrow neck or irregular border or both); and multiple irregular coronary narrowings in series. Type I eccentric lesions were more often seen in patients with stable angina. Type II eccentric lesions were more often seen in patients with unstable angina. These type II lesions were also present in 71% of angina-producing vessels in patients with unstable angina compared to 16% of angina-producing vessels in patients with stable angina. Based on the aforementioned postmortem angiographic and pathologic observations, complex stenoses or stenoses with irregular borders seem to demonstrate plaque rupture, partially occlusive thrombus, or both. Therefore, the type II eccentric lesion or complex lesion likely represents a ruptured atherosclerotic plaque with an associated thrombus. Rupture of this plaque is probably the precondition for the acute progression of coronary artery disease in patients with unstable angina as reported in two previous studies.4,5 This finding of a specific morphology of coronary lesions in unstable angina has been corroborated by other investigators although type II lesions were referred to as complex plaques, intracoronary thrombi, or type "T" lesions.

Angioscopic Studies

Angioscopic studies have provided further insight into the pathophysiology of unstable angina by providing direct visualization of coronary lesions. Thrombi have been found in nearly 90% of patients with unstable angina and rest pain but in no patient with stable angina. Patients with accelerated angina without rest pain have ulcerated plaques without thrombi.13 Forrester et al concluded that coronary artery disease is a dynamic process involving two interlocking cycles: (1) a stable atheroma that progresses to
endothelial ulceration, platelet aggregation, and ~lcer healing and (2) endothelial ulceration, partial thrombosis, complete occlusion, lysis, and thrombus incorporation. The results of their data provide direct in vivo evidence that accelerated angina is associated with plaque disruption and that partially occlusive thrombus is partially responsible for the syndrome of unstable angina with rest pain.

Pathologic Studies

In an attempt to understand the pathophysiology of unstable angina, pathologic studies have provided us with valuable insights into its pathogenesis. Levin and Fallon11 found histopathologic correlations between postmortem coronary angiographic morphology and histologic sections in 73 coronary lesions from patients dying of an acute coronary syndrome. They determined that eccentric lesions with irregular borders, similar in appearance to the type II eccentric stenosis, were histologically "complicated" stenoses exhibiting plaque rupture, plaque hemorrhage, superimposed partially occlusive thrombus, and! or recanalized thrombus. They further stated that these "complicated" lesions were associated with a higher risk of developing an acute myocardial infarction or sudden death than uncomplicated lesions. Falk14 performed postmortem examinations of the epicardial coronary arteries and myocardium in 25 patients with unstable angina who died suddenly and were found to have acute coronary thrombosis. Eighty-one percent of the thrombi analyzed had a layered structure with thrombus material of differing age. This indicates that the thrombus was formed successively by repeated mural deposits that caused progressive luminal narrowing over an extended period of time. This episodic growth of the thrombus was accompanied by intermittent fragmentation of thrombus in 73% of the cases, with peripheral embolization causing microembolic occlusion of small intramyocardial arteries associated with microinfarcts. To explain the pathophysiology of the acute coronary syndromes of unstable anwina, myocardial infarction, and sudden ischemic death, Davies and Thomas15,16 and others17 have proposed a unifying concept which states that progression of coronary disease, secondary to plaque disruption with thrombus formation, is the underlying pathophysiologic process in the majority of patients with all of these syndromes.

Vasospasm

Vasospasm plays an important role in unstable angina and possibly other acute coronary syndromes. This conclusion has been demonstrated by both invasive and noninvasive monitoring of patients with unstable angina during episodes of rest angina. Results showed a primary reduction in coronary blood flow followed by the onset of angina and ST-segment changes in most patients. Unfortunately, the mechanism underlying this primary reduction in coronary blood flow was poorly understood at the time these studies were done. Further studies have introduced new insights into the critical role of platelets, thrombosis, and platelet-derived vasoactive substances as mechanisms of ischemia in unstable angina, enabling investigators to place the issue of vasospasm in unstable angina into perspective. That is, vasospasm is a potential mechanism of ischemia rather than the underlying cause of the syndrome.

In a study by Fitzgerald et al,20 it was demonstrated that 84% of episodes of chest pain in patients with unstable angina were associated with phasic increases in the synthesis of thromboxane and prostacyclin, meaning platelet activation is involved in the evolution of myocardial ischemia in unstable angina. Vasoconstriction and subsequent reduction in coronary blood flow may result when activated platelets attach to a disrupted plaque and release vasoactive substances. Also, platelet aggregates may plug the coronary stenosis and lead to further reduction in stenosis diameter during episodes of myocardial ischemia. Further evidence of the critical role of platelets and thrombosis in the pathogenesis of myocardial ischemia in unstable angina can be derived from the variety of clinical trials demonstrating the benefit of antiplatelet and antithrombotic therapy in preventing myocardial infarction and reducing mortality in patients with unstable angina.21-23

The abnormal vascular tone of atherosclerotic arteries may be related to a deficiency in the production or release of endothelium-derived relaxing factor. 24 In a study by Ludmer, 25 when the vasodilator acetylcholine was administered into the
coronary arteries of patients with both early and advanced atherosclerosis, vasoconstriction was observed. It has also been shown by animal experiments that damaged endothelium responds abnormally to vasoactive substances. Vessels with early atherosclerosis demonstrate an accentuated response to vasoconstrictor substances such as serotonin and thromboxane A2, and an impaired response to vasodilator substances such as bradykinin, acetylcholine, and adenosine diphosphate. Based on these data, it appears that atherosclerosis is associated with an exaggerated vasoconstrictor response triggered by humoral factors due to loss of endothelium-derived relaxing factor. This process may play an important role in the pathogenesis of circadian coronary vasospasm in patients with unstable angina.

Increase in Myocardial Oxygen Demand

As previously mentioned the progression of coronary artery disease and vasospasm leading to a reduction in myocardial oxygen supply are preconditions for the development of unstable angina. Recent evidence suggests that a primary increase in myocardial oxygen demand may precipitate ischemia in a subgroup of these patients. In a study by Langer et al., Holter-ST segment analysis was performed on 196 patients with unstable angina. It was demonstrated that an increase in rate-pressure product preceded the onset of ST segment shifts in 75% of episodes of ST segment shift. They concluded that myocardial ischemia in patients with unstable angina may be mediated in part by an increased myocardial oxygen demand, as defined by an increase in rate-pressure product. However, as the increases in myocardial oxygen demand were usually small, these data are not inconsistent with the concept of plaque disruption and thrombus formation in the pathogenesis of unstable angina. Once a new lesion develops, the supply versus demand balance changes such that even a small increase in myocardial oxygen demand could precipitate ischemia.

Thrombolysis in Unstable Angina

Thrombolytic therapy is an important and successful means of treating myocardial infarction. Thrombolytic agents have been shown to reduce mortality and preserve global and regional left ventricular function if given at least within 6 hours after the onset of symptoms. Pathologic, angiographic, and angioscopic data have demonstrated a mechanism that links the pathophysiology of acute myocardial infarction with other acute coronary syndromes of unstable angina, non-Q wave myocardial infarction, and ischemic death. The underlying mechanism relates, as mentioned above, to disruption of a pre-existing atherosclerotic plaque with the formation of a thrombus upon the exposed plaque contents. The presence of thrombus in patients with unstable angina and the ability of thrombolytic agents to lyse the thrombus has generated much interest. Clinical trials have begun to evaluate the clinical and angiographic efficacy of this modality in the treatment of unstable angina and the closely related syndrome of non-Q myocardial infarction.

Unfortunately, the promise of thrombolytic therapy as a beneficial treatment for patients with unstable angina has yet to be realized. While the presence of a thrombus upon a disrupted plaque would be expected to be amenable to lysis with a thrombolytic agent, studies done thus far, using small numbers of patients, have failed to demonstrate a consistent clinical or angiographic improvement. There may be subtle but important differences in the pathophysiology of unstable angina compared to acute myocardial infarction that account for the lack of a significant benefit for the former syndrome with thrombolytic therapy. The time course of thrombus formation may yield a plaque more refractory to lysis. The amount of acute thrombus formation may be substantially less in unstable angina compared to acute myocardial infarction. Episodic vasomotion and recurrence of angina may not necessarily be affected by even successful thrombolysis in unstable angina. We will have to wait for prospective trials involving large numbers of patients in order to support or refute the role of thrombolysis in unstable angina. In the meantime, other indications for thrombolytic therapy such as an adjunct to angioplasty in unstable angina may develop.

References

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