MECHANISMS OF MYOCARDIAL ISCHEMIA

SAMIR ALAM, MD, FACC

OUR UNDERSTANDING of the mechanisms and consequences of myocardial ischemia has expanded dramatically in the last decade. This paper briefly summarizes fundamental principles of the pathogenesis of myocardial ischemia as they relate to current trends in clinical application. Therapeutic strategies must be based on careful definition of the pathophysiology underlying various clinical surrogates. Stable ischemic syndrome is influenced by the severity of stenosis and the metabolic state of the myocardium. However, dynamic and passive geometric factors at the level of the plaque can exert significant effect on flow dynamics. Functional and dynamic coronary syndromes result from abnormal endothelial function and/or hypersensitivity of vascular smooth muscle. The most threatening features of atherosclerosis are plaque transformation into a thrombogenic surface and occlusive pathology. Atherosclerotic heart disease is a leading cause of death in modern societies. Myocardial ischemia is the principle mechanism which mediates fatal and morbid events in this disease. Ischemia, however, is not pathogenetically uniform and its consequences are variable. Whereas the modern cardiologist is preoccupied with the mechanical aspects of coronary plaque disease, more attention needs to be directed towards the functional and dynamic perturbation of coronary flow which may coexist or be the sole culprit in the genesis of ischemic states. In this paper, we review fundamental principles that are related to the mechanisms and sequelae of myocardial ischemia with brief reference to clinical conditions.

Pathogenesis of Myocardial Ischemia

Myocardial function depends on strict aerobic metabolism for generating adequate energy supply in order to match need. Fatty acids, lactate, and glucose have been established as the major sources of energy. When the oxygen supply of the heart is normal, the rate of glycolysis is inhibited by high levels of ATP and citrate. During anoxia, hypoxia, or mild ischemia, oxidative metabolism ceases, citrate and ATP levels fall, and glycolysis is stimulated. However, during severe ischemia, flow is diminished and the washout of protons and lactate is reduced; their accumulation results in total inhibition of glycolysis. Hence, ATP levels fall critically. The clinical counterpart of these metabolic states is manifested in the markedly different outcome of demand ischemia, often benign and self-limited, whereas supply ischemia, if sustained, results in irreversible cell injury, infarction, or arrhythmic death. The identification of these diverse clinical surrogates is critically significant for adopting effective therapeutic strategies as well as for prognostic implications. Two patterns of ischemia are recognized. Demand or stress-induced ischemia is caused by the disparity of coronary flow and metabolic demand. Impaired flow reserve secondary to coronary obstruction or hypertrophied myocardial disease, despite normal coronary vessels, can lead to cardiac ischemia under conditions of stress - lactate is produced but eliminated, acidosis is mild, ischemia is confined to the vulnerable subendocardial region,
echocardiographic ST depression and impaired diastolic function develop, and arrhythmias are uncommon. In contrast, supply ischemia is secondary to the critical reduction of flow - severe acidosis occurs, glycolysis is inhibited, ATP depletes, and ST elevation develops. Systolic abnormalities and malignant arrhythmias are commonly observed. If ischemia is sustained, irreversible cell death ensues. Supply or transmural ischemia is pathognomonic for total vessel occlusion, either atherothrombosis or vasospasm.

Myocardial blood flow is directly determined by diastolic coronary pressure and inversely related to coronary arteriolar resistance. Alteration of arteriolar vessel tone is mediated by products of ischemia - adenosine, K+, H+, PO2 and PCO2, in addition to sympathetic tone. Relaxation of these vessels permits fourfold flow reserve. A functional, prearteriolar, sphincter is believed to further modulate arteriolar flow. Impaired vasodilation is blamed for a syndrome of ischemic chest pain, reduced flow reserve, objective evidence of ischemia (in less than 40%), and normal coronary vessels - syndrome X.7,8

Pathogenetically, this is a heterogenous entity with several suggested mechanisms, including hyperresponsiveness of resistance vessels, microvascular endothelial dysfunction, increased sympathetic activity, and autonomic dysfunction. It usually follows a benign clinical course with rare occurrence of ischemic events or left ventricular dysfunction. No specific effective therapy has been satisfactory for relief of the symptoms.9-2

Coronary flow is autoregulated for a wide range of perfusion pressure 3,4,6 During severe ischemia or subphysiologic coronary perfusion pressure, autoregulation is ineffective. The flow to the ischemically maximally dilated-vascular bed is directly influenced by perfusion pressure. Interventions aimed at reducing afterload during severe ischemic states, such as the use of ACE inhibitors during acute myocardial infarction, could be deleterious, probably by hypotensive effect or by a coronary steal phenomenon. In spite of extensive literature on the beneficial effects of ACE inhibitors following acute myocardial infarction, efficacy criteria for the selection of subgroups that may benefit from the early use of ACE inhibitors during evolving acute myocardial infarction have not been established. 7 In an experimental canine model of coronary occlusion, we demonstrated that pretreatment with captopril resulted in worsening of ischemia, probably by a steal phenomenon underscoring the superiority of hemodynamic influences and offsetting the potential salutary effects. 18,9

Ischemia, however, may be protective under certain circumstances. Brief periods of acute myocardial ischemia were observed to protect the heart against subsequent episodes of prolonged ischemia.20-23 This phenomenon of preconditioning is believed to be variably mediated, depending on species and activation of adenosine A receptors, a IB receptors, and pertussis toxin-sensitive G protein.23 Although some clinical models such as aortic cross-clamping before establishment of extracorporeal circulation, repeated balloon inflation during angioplasty, and attenuated infarct size following episodes of ischemia may be relevant, the clinical utility of this phenomenon has so far not been demonstrated.20 Myocardial hibernation may also be viewed as a subcellular adaptive mechanism in order to "economize" on critically limited cellular energy stores. Recognition of hibernating but viable myocardium has become a challenging objective because of the potential for recovery following revascularization of the chronic ischemically impaired ventricular function.

Mechanisms of Ischemia

The etiologic and pathophysiological mechanisms which underlie ischemia are heterogenous. The presence of critical atherosclerotic plaque should not lead to an erroneous assumption that more elusive, coexisting, dynamic mechanisms are unimportant - vasomotion can occur superimposed on a fixed obstruction, functional impairment of flow can be secondary to endothelial dysfunction, or "small plaque" and dynamic obstruction due to vasospastic reactivity can occur separately or in combination. These mechanisms could variably and independently contribute to ischemia in the same clinical setting.

Endothelial Dysfunction

Recent evidence suggests that hyperlipidemia impairs endothelial function in the absence of visualized plaque.24-25 Takahashi demonstrated that lipoproteins, in vitro, inhibit endothelial dependent relaxation.26 Cohen et al have shown that impaired endothelium-dependent relaxation occurs in the
coronary arteries of swine that have been fed on a high-cholesterol diet. In normal endothelium, nitric oxide (NO) production causes vasodilation, inhibits platelet aggregation, and attenuates vascular smooth muscle proliferation. Hyperlipidemia seems to interfere with these normal endothelial function. Lefer and Ma have shown that hyperlipidemia leads to a reduction in basal NO production by rabbit coronary artery endothelium. Creager and colleagues have also shown, in humans, that hypercholesterolemia impairs vasodilatation in resistance vessels. It has also been shown that endothelium-mediated vasodilation is attenuated in atherosclerotic human coronary arteries because of either decreased production or increased activation of NO. Correction of lipid abnormality seems to restore normal vasodilator endothelial function. Endothelial dysfunction is believed to play an important role in the pathogenesis of plaque formation, growth, and vulnerability to injury.

**Coronary Artery Spasm**

A vasomotion disorder, related to coronary (and systemic) disease of vascular smooth muscle, is characterized by focal or diffuse narrowing of the epicardial coronary arteries. Resistance vessels have also been shown to be affected by vasomotion disorder, even in the nonvasospastic vascular beds. The relationship of focal spasm to ultimate progression of atherosclerosis is a relevant issue that has been suggested but not uniformly confirmed. Hyperresponsiveness of coronary arteries to ergonovin, serotonin, and acetylcholine have been consistently demonstrated. Calcium blockers have been particularly effective in preventing myocardial infarction and sudden death. Increasing incidence of cocaine-related vasospastic events is presently being reported.

**Plaque Stenosis**

A major consequence of atherosclerosis stems from the mechanical effect of the plaque and related hydraulic interactions on flow. Despite significant, subcritical stenosis, coronary blood flow is maintained by the ability to relax arteriolar resistance vessels. When stenosis is severe, vasodilation is maximal, coronary reserve is exhausted, and coronary resistance rises exponentially so that plaque-site resistance is triple when stenosis increases from 80% to 90%. Therefore, platelet aggregation and changes of coronary vessel tone, even small thrombus formation or passive collapse of the coronary vessel, can lead to precipitous rise of resistance and diminished flow. During exercise there is increased flow, and according to the principles of fluid mechanics, pressure is lost to turbulence. Hence, intraluminal coronary pressure tends to fall, resulting in vessel collapse and reduction in stenosis vessel diameter. Agents such as calcium blockers and ACE inhibitors (as commonly and empirically prescribed in combination for the treatment of stable anginal syndromes) can potentially amplify these local changes and have been shown, in small clinical trials, to exert variable and unpredictable influence on exercise-induced ischemia.

Similarly, we observed no beneficial effect and occasionally worsening of ischemia in 16 nonhypertensive patients who were tested on the treadmill before and after nonhypotensive dose of ACE inhibitors.

**Plaque Interaction**

An important manifestation of atherosclerosis is plaque interaction with the adjacent vessel wall, mediated by endothelial dysfunction or injury and superimposed platelet aggregation. Dynamic and/or mechanical alterations of plaque-site stenosis can thus develop which results in silent ischemia, angina, unstable syndrome, myocardial infarction, or sudden death. This mechanism probably explains several clinical observations such as "walk through" and "variable threshold", stable angina, as well as the occurrence of silent rest ischemia in asymptomatic patients and those with stable ischemic syndromes. Acute ischemic syndromes are the result of intrinsic injury to the plaque and covering endothelium. A cascade of events are consequently triggered, resulting in more intense expression of platelet deposition, vasospasm, and thrombus formation. Because culprit plaques are often mild-moderate in severity (50%), they are elusive and their behavior is unpredictable.

**Conclusion**

Ischemia is the culprit pathophysiologic link which bridges coronary atherosclerosis pathology with fatal and non-fatal clinical consequences of
coronary disease. Neither the cause nor the nature of ischemia is uniform. The assessment and hence therapeutic strategies targeting ischemia must be based on the exact elucidation of the mechanisms underlying the pathogenesis of myocardial ischemia; the dynamic and pathologic states leading to an imbalance between myocardial demand and flow or, more dangerously, the reduction of flow must be carefully sought and fully established for effective and definitive therapy. The coexistence of pathologic, dynamic, and functional coronary vascular factors is a real possibility under many clinical or pharmacologic conditions.

References
