Editorial Comment

The Microcirculation in Coronary Ischemia
Are Native Anticoagulant Mechanisms a Path to New Therapies?

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The evolving concept that coronary artery patency after myocardial infarction is associated with improved short- and long-term survival and left ventricular function has intensified efforts to open thrombosed vessels. The importance of maintaining vessel patency has also become clear. Ohman et al found that patients with documented reoclusion had more complicated hospital courses, higher in-hospital mortality rates, and worse infarct zone function. Efforts to maintain patency have been hampered by a significant rate of reoclusion—approximately 12–18% after successful thrombolytic therapy for acute myocardial infarction. Because this rethrombosis occurs in the setting of a systemic fibrinolytic state, therapeutic efforts have been directed toward inhibition of platelet activation and aggregation. This has focused attention on anticoagulant mechanisms native to the vessel itself.

See p 293

Two endothelium-dependent anticoagulant mechanisms have been shown to be active in vivo. One mechanism involves heparinlike molecules present on the endothelial cell surface and in the extracellular matrix that accelerate the inactivation of coagulation proteases by antithrombin III. The other mechanism involves the anticoagulant effect of thrombomodulin. Thrombomodulin binds to thrombin, decreasing its ability to stimulate clot formation (by platelet activation and conversion of fibrinogen into fibrin). In addition, thrombomodulin-bound thrombin is capable of activating protein C. The presence of activated protein C (APC), a serine protease that enzymatically cleaves coagulation factors Va and VIIIa, inhibits further thrombin formation. Because of the strong association between protein C deficiency and an increased incidence of thrombosis, as well as the documented efficacy of exogenously administered APC to inhibit thrombus formation in both microcirculatory and arterial thrombosis models without impairing primary hemostasis, APC has been an area of active research. In fact, recombinant APC has recently been shown to inhibit arterial thrombosis in a primate model.

Extending this research effort on APC, the article in this issue of Circulation by Snow et al provides important new insights into APC function. Using a porcine model of coronary ischemia, these authors present three new findings regarding APC: 1) α-thrombin is a potent activator of protein C in the coronary circulation, 2) both occlusion and ischemia cause rapid activation of protein C, and 3) recovery of left ventricular function (and even survival) is enhanced by administration of exogenous APC and diminished by pretreatment with an antibody against APC.

Two important implications may be drawn from these findings. First, in contrast with previous studies in conduit arteries, the effect of APC in this model is mediated primarily in the microcirculation. The data indirectly suggest that microvascular thrombi play an important role in disease states associated with myocardial ischemia and dysfunction such as unstable angina and acute myocardial infarction. Second, it appears that APC administered intravenously may have potential therapeutic efficacy in the treatment of myocardial ischemia, particularly secondary to coronary artery thrombosis.

The role of the microvasculature (vessels smaller than 250 μm in diameter) in human myocardial dysfunction has been underappreciated. Several new concepts, however, indicate its potential importance in a variety of disease processes. It has become clear that hypercholesterolemia and atherosclerosis markedly alter endothelial cell function. Initially, epicardial coronary arteries were found to have impaired endothelium-dependent relaxation that was thought to be secondary to decreased endothelium-derived relaxing factor (EDRF) production. Harrison and colleagues extended these observations to the microcirculation. They observed in hypercholesterolemic cynomologus monkeys (on a 0.7% cholesterol diet for 18 months), that coronary microvessel (122–220 μm) relaxations to bradykinin and the calcium ionophore A23187 were reduced and that acetylcholine provoked a contractile response. Thus, one may...
suppose that the atherosclerotic microcirculation of the human myocardium would also exhibit dysfunctional vasodilator responses.

Several studies indicate that endothelial dysfunction may be dynamic and reversible. Two model systems have been used to study the effects of acute endothelial cell injury on EDRF release. Rosenblum and colleagues\(^{20}\) caused local damage by intravenous administration of Evans blue dye followed by helium-neon laser irradiation. This treatment caused local thermal injury with decreased EDRF production and release. It is noteworthy that the loss of EDRF was transient and endothelium-dependent relaxation recovered within 4 hours. Other investigators\(^{21,22}\) have demonstrated that global myocardial ischemia followed by reperfusion abolished acetylcholine-induced dilation. Application of topical superoxide dismutase plus catalase or desferoxamine preserved endothelium-dependent relaxation, arguing for an important role for free radicals.\(^{23}\) Harrison and colleagues\(^{24}\) have shown that ischemia followed by reperfusion appeared to have a more profound effect on the endothelium-dependent relaxation of coronary microvessels than on relaxation of larger epicardial arteries. In a canine model (1 hour of ischemia followed by 1 hour of reperfusion), the endothelium-dependent relaxations to acetylcholine, ADP, and A23187 were significantly impaired in microvessels, whereas the epicardial vessel responses were unaffected. Thus, an important consequence of ischemia/reperfusion is loss of endothelium-dependent vasodilator function.

It has also become clear from in vitro studies that during hypoxia, the microvascular endothelium also undergoes dramatic alterations in its surface coagulant properties. Stern and coworkers\(^{25}\) have shown that hypoxemic endothelium exhibits an 80–90% decrease in the natural anticoagulant factor thrombomodulin, and a new procoagulant factor X activator appears as well.\(^{26}\) Furthermore, release of EDRF by ischemic endothelium is significantly impaired, and EDRF exerts a direct antithrombotic effect by inhibiting platelet aggregation.\(^{27}\) Thus, it appears that the endothelium of the microcirculation is extraordinarily sensitive to ischemia, responding with loss of natural anticoagulant and vasorelaxing properties.

The present article by Snow et al\(^{16}\) provides some of the strongest data yet presented that microvessel endothelial function contributes to global myocardial function during ischemia. Their findings that administration of APC improved both left ventricular function and survival argue that dynamic changes in the natural anticoagulant mechanisms of the microcirculation play an important role in the myocardial response to ischemia. Most importantly, this suggests a potential therapeutic role for agents such as recombinant APC. APC appears to have a distinct advantage over other agents that inhibit platelet aggregation, because at therapeutically effective doses there appears to be no significant inhibition of normal hemostatic plugs.\(^{14,15}\) The use of APC may therefore avoid the complications of bleeding that have occurred with other agents that block thrombin formation. Parenthetically, because APC works by a different mechanism than currently available therapies that increase fibrinolysis, it may also have an important adjuvant role. Recent studies have shown that infusion of urokinase combined with APC results in a net additive effect of the antithrombotic activities of each agent.\(^{28}\) It may be possible, then, to design a treatment regimen with APC and other agents that optimizes reperfusion, vessel patency, and integrity of the microcirculation.

Study of the microcirculation in coronary artery thrombosis has been neglected because it is invisible angiographically. The present work illustrates the importance of considering this aspect of coronary circulation in our efforts to devise new therapies. Because loss of endothelial vasodilator function during ischemia/reperfusion may be transient,\(^{29}\) it is also possible that the changes in procoagulant properties are reversible. The fact that platelet microthrombi have been found in patients with unstable angina has been assumed to represent distal embolization.\(^{29}\) The present study suggests that local platelet deposition due to impaired native anticoagulant mechanisms may be equally important. The findings of Snow et al\(^{16}\) suggest that further investigation of the unique properties of the cardiac microcirculation may provide new insight into therapeutic approaches for salvaging ischemic myocardium.

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References


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