CONSTRICITION AND DILATATION IN
ATHEROSCLEROTIC AND HYPERTENSIVE ARTERIES

Donald D. Heistad, J. Antonio G. Lopez, Frank M. Faraci, and Mark L. Armstrong

Department of Internal Medicine, VA Medical Center and University of Iowa College of Medicine, Iowa City, Iowa

INTRODUCTION

We will emphasize three points that pertain to approaches to quantification of changes in atherosclerotic lesions.

First, changes in responsiveness of arteries to vasoactive substances occur very early in atherosclerosis. Thus, examination of vascular reactivity may be a sensitive way to detect changes in atherosclerotic lesions. It seems likely that examination of vascular reactivity may be more sensitive than measurement of changes in vascular diameter and perhaps wall thickness in detection of early and moderately severe atherosclerosis.

Second, we will mention briefly the changes in vascular responses in chronic hypertension. Hypertension alters vascular responses, but mechanisms of the changes are quite different from those observed in atherosclerotic arteries.

Third, we will discuss effects of regression of atherosclerosis on vascular reactivity. It appears that studies of vascular responsiveness may be a sensitive approach during regression as well as progression of atherosclerosis.

In this era, which may be characterized as the dawn of effective treatment of hypercholesterolemia, a critical question is whether treatment of hypercholesterolemia has beneficial hemodynamic consequences. Perhaps the major implication of this paper is that, in detection of regression of atherosclerosis, examination of vascular reactivity may be far more sensitive than examination of structural changes by angiography.

VASCULAR RESPONSES TO PLATELETS

Several approaches indicate that atherosclerosis alters vascular reactivity. Responses to constrictor and dilator stimuli are altered in atherosclerotic arteries in vitro (1-5), in experimental animals in vivo...
Exaggeration of vasoconstrictor responses, combined with impairment of vasodilator responses, predispose to vasospasm, which is an important complication of atherosclerosis (8).

A major hypothesis concerning the pathophysiology of vasospasm focuses on the role of platelets (9). The hypothesis is that platelets adhere to damaged endothelium over atherosclerotic lesions, and the platelets aggregate and release their vasoactive products. We have examined effects of atherosclerosis on vascular responses to ADP, serotonin, and thromboxane, which are the three major products that are released by platelets.

When platelets aggregate in a normal artery, ex vivo, the potent vasodilator effects of adenosine diphosphate (ADP) usually mask the vasoconstrictor effects of thromboxane and the variable effects of serotonin, so that the net response is vasodilatation (10). Activation of platelets also produces vasodilatation in vivo, but we have performed several studies which indicate that atherosclerosis profoundly alters responses to vasoactive products that are released by platelets.

First, we examined vascular responses to injection of ADP, serotonin, and thromboxane. Several experimental approaches were used including studies of a limb that was perfused in vivo (6,11), measurement of blood flow with microspheres (12,13), and measurement of microvascular pressure (12). Vasodilator responses to ADP are impaired by atherosclerosis, vasodilator responses to serotonin are reversed to vasoconstriction, and vasoconstrictor responses to thromboxane are augmented (6,11). Vascular responses to these agonists are altered in atherosclerotic cynomolgus monkeys in several vascular beds: the limb (6,11), coronary arteries (12), and cerebral and ocular circulation (13). These studies indicate that vascular responses to ADP, serotonin, and thromboxane are altered by atherosclerosis in a direction that would favor augmented vasoconstriction or vasospasm when platelets aggregate.

Second, we have infused purified bovine collagen in the perfused limb of monkeys, to produce aggregation of platelets in vivo (14). Infusion of collagen produced vasodilatation in normal monkeys, presumably from release of ADP from platelets. In atherosclerotic cynomolgus monkeys, that were fed an atherogenic diet for 18 months, collagen produced marked constriction of large arteries. The constrictor effect was prevented by pretreatment of the monkeys with indomethacin. Thus, activation of platelets in vivo produces constriction of large atherosclerotic arteries. These findings support the hypothesis that, when platelets are activated in vivo, they may produce constriction or perhaps spasm of atherosclerotic arteries.

VASCULAR RESPONSES TO LEUKOCYTES

There are many leukocytes (primarily monocyte-macrophages) in atherosclerotic lesions (15). Blood-borne monocytes adhere to endothelium, and monocyte-macrophages are present within atherosclerotic lesions. A major hypothesis is that growth factors that are released by monocyte-macrophages may stimulate cellular migration and proliferation and thus play a critical role in the development and progression of the atherosclerotic lesion (15).

We have proposed a new hypothesis in relation to the role of leukocytes in atherosclerosis. The hypothesis is that leukocytes may contribute to spasm of atherosclerotic arteries.

The initial experimental evidence for this hypothesis was based on