

HOSPITAL PHYSICIAN®

CARDIOLOGY BOARD REVIEW MANUAL

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The *Hospital Physician Cardiology Board Review Manual* is a peer-reviewed study guide for fellows and practicing physicians preparing for board examinations in cardiology. Each bimonthly manual reviews a topic essential to the current practice of cardiology.

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Association for Hospital
Medical Education

Inflammation, Infection, and Coronary Atherosclerosis

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Cover Illustration by mb cunney

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Inflammation, Infection, and Coronary Atherosclerosis

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INTRODUCTION

Atherosclerosis, the pathologic basis of coronary artery disease (CAD) and ischemic stroke, is the leading cause of death and disability in the Western world. In the United States, atherosclerosis reportedly affects 1 in 4 persons and causes approximately 42% of all deaths. Nearly half of these deaths are due to atherosclerotic CAD. Although the pathological process of coronary plaque development is well understood, the underlying etiology remains unclear. Classical atherogenic risk factors include cigarette smoking, hypercholesterolemia, diabetes mellitus, hypertension, and a positive family history of CAD. However, up to 30% of patients presenting with myocardial infarction (MI) have none of these risk factors.¹ In addition, the exact mechanisms by which these factors contribute to the development of atherosclerosis are still largely unknown. Given these uncertainties, it is important to search for additional risk factors that may play a role in the etiology of atherosclerosis.

Recent progress in understanding the pathogenesis of atherosclerosis has uncovered the central role of inflammation in atherosclerosis.^{2,3} Under normal conditions, the endothelium does not bind white blood cells. Shortly after experiencing an initial insult, the “injured” endothelium begins to express adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and selectins. The endothelium also secretes chemoattractant molecules (ie, chemokines) that attract circulating inflammatory cells to the endothelium and facilitate the binding of the inflammatory cells to the adhesion molecules.⁴ Subsequently, these white blood cells migrate further into the subendothelial space. Activated monocytes, platelets, and T lymphocytes secrete a variety of products, such as interleukin (IL)-1, interferon α , and tumor necrosis factor- α (TNF- α). Macrophages internalize oxidized low-density lipoproteins (LDL), leading to an accumulation of intracellular cholesterol. A fibrous cap forms as the atherosclerotic plaque matures, covering the lipid core. Inflammatory cells se-

crete matrix metalloproteinases that are capable of digesting collagen and thinning the fibrous cap. Interactions between T lymphocytes and macrophages also increase the expression of the potent procoagulant tissue factor. Erosion and eventual rupture of the fibrous cap may trigger formation of superimposed thrombus, leading to the clinical manifestations of acute coronary syndromes (ACS), such as MI, or unstable angina.

INFLAMMATORY MARKERS AND CAD

It has long been recognized that acute MI increases markers of inflammation, such as the erythrocyte sedimentation rate and levels of C-reactive protein (CRP). It is now evident that chronic inflammation plays a central role in the development and progression of atherosclerosis, and investigators have sought to translate this knowledge into clinical practice. Plasma levels of several mediators of inflammation have been evaluated as a means for measuring the severity of inflammation and predicting future cardiac events (**Table 1**).

C-REACTIVE PROTEIN

The most extensively studied inflammatory marker is the acute phase reactant CRP. CRP is produced by hepatocytes under the influence of cytokines such as IL-6 and TNF- α . A standardized high sensitivity assay (hs-CRP) for measuring CRP levels is widely available. Primary prevention studies among apparently healthy men and women have demonstrated the predictive value of CRP levels in assessing cardiac risk. In the Physician’s Health Study,⁵ among apparently healthy men, the baseline level of CRP predicted the long-term risk of a first MI, ischemic stroke, peripheral vascular disease, and all-cause mortality. This correlation persisted after adjustment for age, smoking, lipid levels, blood pressure, and diabetes. The predictive value of CRP was compared with LDL cholesterol in a prospective nested case-control study among 28,263 apparently healthy postmenopausal women in the Women’s Health Study.⁶ Increasing quartiles of baseline CRP