Is Coronary Artery Disease an Infectious Disease?

In 1913, Anitschkow first described the development of atherosclerotic vascular lesions in rabbits fed a high cholesterol diet. For over 80 years, this relationship of cholesterol intake and atherosclerosis has been inviolate. Since then, extensive epidemiologic studies have shown that in addition to hypercholesterolemia, the most common risk factors for coronary artery disease are cigarette smoking, hypertension, and diabetes mellitus. However, these risk factors are absent in about 30% of patients with myocardial infarction (MI). Until recently, most epidemiologic studies focused on known risk factors, and scant attention was devoted to the study of patients without classical risk factors. These patients were often thought to be anomalous, exceptional, or with “corrected risk factors.” This group may constitute a significant number of the 1.5 million hospital admissions and 900,000 deaths that occur annually in the United States from coronary artery disease.

Recent studies have shown that some patients without classical risk factors have evidence of an exaggerated inflammatory process that may trigger vascular occlusion. The mechanism has not been completely elucidated. In 1966, Constantinides and Friedman and Van den Bovenkamp independently detailed the histologic features of coronary artery thrombosis. Each study noted macrophage infiltration of the arterial plaques, leading Friedman and Van den Bovenkamp to term these lesions “atheromatous abscesses.” Disruption of the atherosclerotic plaque (with subsequent platelet aggregation, thrombosis, and coronary occlusion) is now well established as the cause of most MI. Only recently has attention been turned to the intense inflammatory response noted by van der Wal et al. Clinical signs of this inflammatory process, such as elevated sedimentation rate, C-reactive protein, and amyloid A protein, have been found in patients with acute infarction and unstable angina.

The presence of circulating activated T lymphocytes in patients with unstable angina is an indicator of antigenic stimulation that is part of the inflammatory response. Recently, microorganisms have been incriminated as the “triggering antigen” in this reaction. Chlamydia pneumoniae, a common human respiratory pathogen, has widespread geographic distribution and affects people of all ages. It is thought to be responsible for 5% of acute bronchitis cases and 10% of cases of pneumonia. C. pneumoniae is the third species in this genus of obligate intracellular bacterial parasites (C. psittaci, C. trachomatis). Grayston et al. described it in 1986 and called it TWAR (Taiwan acute respiratory agent), due to the clinical history associated with the first two isolates. Chlamydia species require cell culture for isolation, and thus serology and direct examination of clinical specimens have been the only practical methods available for the study of the organism. Recent use of microimmunofluorescence and polymerase chain reaction (PCR) for antigen amplification and detection has enhanced our ability to detect and characterize Chlamydia species clinically and epidemiologically.

Chlamydia pneumoniae has been detected in atheromatous vascular tissue of aortic aneurysms, atheromatous coronary artery lesions, and non-rheumatic stenotic aortic valves. Kawasaki’s arteritis and Takayasu’s arteritis might have infectious origins, and C. pneumoniae has been considered a possible agent. Serologic evidence of recent Chlamydia exposure also has been demonstrated in patients with acute MI (AMI). In this issue of CHEST (see page 309), Blasi and colleagues report a retrospective study that gives further support to the possibility that C. pneumoniae infection is an “inducer” or “enhancer” of plaque destabilization and disruption. They also have shown that reinfection may “trigger” AMI. In a series of 61 patients admitted with AMI, pharyngeal swabs were obtained, and nested PCR was used to detect a ribosomal RNA antigen specific for C. pneumoniae. Microimmunofluorescence was used to determine IgG, IgA, and IgM titers on sera from acute and convalescent cases. Criteria were established for an acute first infection, a past chronic infection, and a reinfection. Serologic evidence of past infection with C. pneumoniae was present in 35 of 61 patients presenting with AMI, compared to 18 of 61 in the control population. Serologic evidence of reinfection was present in 12 patients with AMI, which supports the idea of a specific precipitating event. Blasi and colleagues are among the first to explore this idea.
They propose that the “triggering agent” for the MI was reinfection with *C. pneumoniae*.

Whether the localized inflammation associated with atherosclerotic plaques predisposes a patient to opportunistic infection, or it is the infection that causes the initial intimal defect leading to plaque formation is not known. Thus, the role of infectious agents such as bacteria, viruses, rickettsiae, chlamydiae, or fungi in coronary vascular disease requires further investigation. The possibility of more specific, effective, and perhaps preventative therapy may lie within this hypothesis. Recently, Gupta and associates found that azithromycin therapy for patients with evidence of *C. pneumoniae* post-MI decreased the inflammatory response compared to patients treated with placebo.

Many facets of diagnosis and treatment may be affected by these findings. For example, aspirin administration is well established as beneficial therapy in unstable angina and AMI. This benefit is known to result from the effect of aspirin on the cyclooxygenase arm of the arachidonic acid cascade, ultimately decreasing platelet adhesion. Considering this new information, reduction of the vascular inflammatory response may be an important additional action of aspirin, one that results in a reduction in the inflammatory response and a decrease in the size of the atherosclerotic plaque. Much more investigation is necessary in this fascinating area of atherogenesis.

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Aerosols for the Intubated
Cultivating the Rose

In this issue of CHEST (see page 484), Torres and colleagues report that both metered-dose inhaler (MDI) and nebulized β-agonist can be delivered to achieve therapeutic effect in intubated, mechanically ventilated infants with bronchiolitis. Previous studies have suggested that MDI can be effective for intubated adults when proper techniques of administration and an in-line spacer are used. The current study provides two techniques that can be used to effectively deliver therapeutic aerosols to infants in whom small endotracheal tubes significantly impede aerosol delivery. Note that these data cannot be extrapolated to assume that all MDIs and nebulizers are effective. Rather, the specific delivery techniques and devices used in this study were effective—in aerosol delivery, the devil is in the details, as upwards of 100 puffs of MDI can be ineffective with certain delivery devices.

Since MDIs reduce medication and labor costs compared to nebulizers, MDIs are preferred at many hospitals. Nevertheless, it must be emphasized that if proper techniques are not used, therapeutic effect is limited, which is obviously cost ineffective! Since numerous ventilator- and patient-dependent