Mechanisms of Acute Coronary Syndromes

TO THE EDITOR: In his review article about the mechanisms of disease of acute coronary syndromes and their potential therapies, Libby (May 23 issue) does not refer to the role of hyperglycemia, although the association between dysglycemia and atherosclerosis has been clearly shown. Hyperglycemia is an important factor in cardiovascular damage, working through different mechanisms such as the activation of protein kinase C, polyol and hexosamine pathways, and the production of advanced glycation end products. Moreover, hyperinsulinism has been established as an important factor associated with the occurrence of new cardiovascular events in patients with a first myocardial infarction. The common mechanisms that contribute to insulin resistance and endothelial dysfunction also include gluotoxicity, lipotoxicity, and inflammation, which are correlated with oxidative stress and result in an increased risk of cardiovascular events. Hence, appropriate glycemic control, in association with the treatment of dyslipidemia and other pro-oxidative conditions, is necessary to counteract oxidative stress in patients with cardiovascular diseases, such as acute coronary syndromes.

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mendelian randomization analysis from our institution, emphasizing the importance of primary prevention strategies for coronary artery disease.

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TO THE EDITOR: In his presentation of the mechanisms of acute coronary syndromes and their implications for therapy, Libby does not explain why 63% of coronary plaques rupture at the shoulder region and only 37% in the center of the cap. 

By contrast, 94% of carotid plaques rupture around the midpoint and between the midpoint and the shoulder, and only 6% at the shoulder region. Persons who die during exertion have coronary plaque rupture mainly in the midpoint of the fibrous cap, in contrast to those who die at rest and who have plaque rupture at shoulder regions.

Ultrastructurally, the junctions between endothelial cells that line human plaques are often open, whereas the junctions over the normal arterial wall are usually closed. This allows inflammatory cells to penetrate selectively into these particular plaque areas.

Libby did not refer to the activation of matrix metalloproteinases (MMPs) by mast-cell–derived proteases, which may be an important mechanism in the destabilization of atherosclerotic plaque. Immunocytochemical analyses have identified significantly higher numbers of tryptase-containing mast cells and cells expressing MMP-1 and MMP-3 in the shoulder regions of atherosclerotic plaques than in the tunica media of control nonatherosclerotic arteries.

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THE AUTHOR REPLIES: Gómez-Arbeláez and López-Jaramillo consider the role of glycemic control and countering oxidative stress in patients at risk for acute coronary syndromes. Dysglycemia and associated metabolic derangements certainly associate with cardiovascular risk. My review, however, focused primarily on therapeutic opportunities supported by rigorous clinical evidence. Glycemic control indeed limits the microvascular complications of diabetes. Yet, more recent clinical trials — conducted in the statin era — show that strict glycemic control confers at best a slight reduction in the risk of acute coronary syndromes, while augmenting the risk of hypoglycemia. Moreover, despite preclinical evidence pointing to oxidative stress as a therapeutic target in atherosclerosis, a large and well-conducted trial of antioxidant vitamins and of one pharmacologic antioxidant agent did not show a reduction in the risk of cardiovascular events. These results have called into question the role of strict glycemic control or antioxidant therapy in the prevention of acute coronary syndromes.

Reddy and Jagadeesh emphasize the importance of biomechanical factors in the regulation of inflammation and fibrous-cap stability. I agree wholeheartedly. Current data highlight the importance of shear stress in regulating the atheroprotective functions of the endothelium. In regions of disturbed flow, arteries lose these protective
functions and show heightened susceptibility to atheroma development and conditions that would favor thrombus accumulation.\(^3\) I fully endorse their assertion of the importance of primary prevention strategies for coronary artery disease.

Kounis cites the pioneering morphologic studies by Constantinides and Harkey that showed open junctions between endothelial cells over human plaques. Since these classic studies, substantial data have highlighted qualitative abnormalities in endothelial function rather than desquamative injury, or physical discontinuities between junctions, as a mechanism of inflammatory-cell recruitment.\(^3\) The expression of selective adhesion molecules on the surface of endothelial cells that have undergone activation by risk factor–related stimuli, and local elaboration of chemotactant molecules, lead to leukocyte accumulation in lesions, according to current evidence. I agree completely regarding the potential contributions of mast cells and their proteases to atherogenesis — indeed, genetic studies in mice rigorously implicate mast cells in experimental atherogenesis.\(^4\)

I further concur with the points raised regarding the roles of mast-cell–derived proteases in the activation of MMPs. In addition to the mast-cell–derived enzymes chymase and tryptase, other serine proteases, including some involved in blood coagulation, such as plasmin and thrombin, can also activate the zymogen forms of MMPs.\(^5\)

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**Middle East Respiratory Syndrome Coronavirus Infections in Health Care Workers**

**TO THE EDITOR:** A majority of the 94 cases of Middle East respiratory syndrome coronavirus (MERS-CoV) infection that have been reported to date have occurred in Saudi Arabia. Patients with this infection have presented with serious respiratory disease and have required hospitalization.\(^1,2\) However, there have been case reports of less severe disease within family\(^3,4\) and hospital\(^2\) clusters, and the clinical spectrum of MERS-CoV infections may extend to asymptomatic and subclinical cases. Therefore, the epidemiologic and clinical characteristics of this infection need further definition. The patterns of the spread of MERS-CoV among family\(^3,4\) and hospital\(^2\) clusters suggest that transmission occurs through droplets or contact. We previously reported two cases of MERS-CoV infection in health care workers,\(^2\) one of which was fatal.

The presence of asymptomatic or subclinical MERS-CoV infections in the community or among health care workers could have important public health implications, since these infections may be sources of transmission to close contacts in the community or to patients with coexisting medical conditions. The close proximity of health care workers to patients and the handling of human biologic material (sputum, respiratory secretions, feces, urine, or blood) may increase the risk of transmission, and health care workers may be particularly at risk for MERS-CoV infections.

The Saudi Arabian Ministry of Health routinely screens all close contacts of patients in whom MERS-CoV infection has been diagnosed, and more than 3000 people have been screened to date. We recently identified seven health care workers with MERS-CoV infection (two of whom were asymptomatic and five of whom had mild upper respiratory tract symptoms) through screening of single sample nasopharyngeal swabs