Hospital prognosis of moderate to severe pericardial effusion (MPE; ≥10 mm) in ST-elevation myocardial infarction is largely unknown, and its management poses a therapeutic dilemma because not all patients benefit from emergency surgery aimed at treating an underlying free-wall rupture. Data from 446 ST-elevation myocardial infarction patients, 228 with MPE—88 with cardiac tamponade (CT) and electromechanical dissociation (EMD), 44 with CT and hypotension, and 96 without initial CT—and 218 with small PE (5 to 9 mm), were compared. CT patients showed larger PE (P<0.001) than those without initial CT; 85% of those with CT+EMD and 86% with CT plus hypotension were treated with pericardiocentesis, and 10% and 21% were treated with a surgical repair, respectively. Among MPE patients, 30-day mortality was 43% and was higher in those with CT+EMD (operated, 89%; nonoperated, 85%) than in those with CT plus hypotension (22% and 11%, respectively; P<0.001) and those without initial CT (17%; P<0.001). It was also higher than in patients with small PE (10%; P<0.001). Death was attributable to cardiac rupture in 83% of patients with CT+EMD, 7% with CT plus hypotension, and 8% with MPE without initial CT, and it occurred late (≥7 days) in 14%, 67%, and 100%, respectively. Thus, MPE carries an increased mortality, which is highest in patients with CT+EMD. In those with CT plus hypotension, however, mortality is considerably lower after pericardiocentesis, and subsequent management may be individualized because a conservative approach is often successful. Importantly, MPE patients without initial CT are not free from late rupture and deserve further investigation. See p 1902.

### Relationship of Echocardiographic Dyssynchrony to Long-Term Survival After Cardiac Resynchronization Therapy

This study demonstrated the association of echocardiographic dysynchrony with long-term survival after cardiac resynchronization therapy (CRT). We studied 229 consecutive patients with routine CRT indications (symptomatic heart failure, reduced ejection fraction, and widened QRS ≥120 milliseconds), of whom 210 (89%) had baseline echocardiographic dyssynchrony data available. Dyssynchrony was prespecified as tissue Doppler longitudinal velocity opposing-wall delay ≥65 milliseconds, 12-site SD (Yu Index) ≥32 milliseconds, speckle tracking radial strain anteroseptal-to-posterior wall delay ≥130 milliseconds, or pulsed Doppler interventricular mechanical delay ≥40 milliseconds. Of 210 patients, there were 62 unfavorable events over 4 years after CRT: 47 deaths, 9 transplantations, and 6 left ventricular assist device implantations. All echocardiographic dyssynchrony indexes were significantly associated with a more favorable long-term prognosis than for patients without dyssynchrony, except tissue Doppler velocity opposing-wall delay became significant at ≥80 milliseconds. When adjusted for covariates of ischemic pathogenesis and QRS width, the Yu Index and speckle tracking radial strain remained independently predictive of outcome. Subgroup analysis demonstrated that patients with narrower QRS width of 120 to 150 milliseconds who lacked radial dyssynchrony had a particularly poor survival. Although this study has identified the absence of echocardiographic dyssynchrony as a marker for a less favorable prognosis in patients who undergo CRT for routine indications, the potential influence of CRT on outcome in patients without dyssynchrony remains unknown. These observations strongly support the association of echocardiographic dyssynchrony with long-term patient outcome after CRT. See p 1910.

### High-Density Lipoprotein Suppresses the Type I Interferon Response, a Family of Potent Antiviral Immunoregulators, in Macrophages Challenged With Lipopolysaccharide

The cardioprotective effect of high density lipoprotein (HDL) is thought to involve the clearance of cholesterol from lipid-laden macrophages in the artery wall. However, recent evidence suggests that HDL might also inhibit atherogenesis by combating inflammation. To identify potential antiinflammatory mechanisms, we challenged macrophages with lipopolysaccharide, an inflammatory microbial ligand for Toll-like receptor 4. We found that HDL inhibited the expression of many genes normally induced by lipopolysaccharide. Unexpectedly, expression of inflammatory cytokines like tumor necrosis factor-α and interleukin-6 was not inhibited by HDL. Instead, the major target was the type I interferon response pathway, a family of potent viral immunoregulators controlled by Toll-like receptor 4 and the TRAM/TRIF signaling pathway. Moreover, the ability of HDL to inhibit gene expression was independent of cellular cholesterol stores. Our observations suggest that TRAM translocates to intracellular compartments when macrophages are exposed to HDL. This in turn impairs subsequent signaling by Toll-like receptor 4 and TRIF, which plays a key role in triggering the type I interferon response. Our results may be physiologically relevant because mice deficient in the major protein of HDL exhibited 6-fold higher levels of interferon-β, a key regulator of the type I interferon response, than did wild-type mice when the animals were infected with a Gram-negative bacterium. We conclude that HDL inhibits a subset of lipopolysaccharide-stimulated macrophage genes that regulate the type I interferon response and that its action is independent of sterol metabolism. These findings raise the possibility that regulation of macrophage genes by HDL might link innate immunity and cardioprotection. See p 1919.

### Comparison Between Transcatheter and Surgical Prosthetic Valve Implantation in Patients With Severe Aortic Stenosis and Reduced Left Ventricular Ejection Fraction

Patients with severe aortic stenosis and reduced left ventricular ejection fraction have a poor prognosis with medical treatment but a high operative mortality when treated surgically. These patients pose an important challenge with regard to therapeutic management because they require a valve replacement procedure that ensures optimal valve hemodynamics with complete relief of left ventricular outflow obstruction while minimizing the operative risk. The results of the present study suggest that transcatheter aortic valve implantation may achieve both of these goals. The most important finding of this study is that, despite a much worse risk profile at baseline, transcatheter aortic valve implantation was associated with faster and better recovery of left ventricular ejection fraction compared to surgical aortic valve replacement. This benefit may be due, at least in part, to better periprocedural myocardial protection and superior prosthetic valve hemodynamics. Hence, transcatheter aortic valve implantation may provide a good alternative to surgical aortic valve replacement in patients with severe aortic stenosis and depressed left ventricular systolic function considered at high or prohibitive surgical risk, which includes patients with severe comorbidities, small
aortic root, and/or lack of myocardial contractile reserve on dobutamine stress test. See p 1928.

Effects of HIV Protease Inhibitors on Progression of Monocrotaline- and Hypoxia-Induced Pulmonary Hypertension in Rats

Pulmonary arterial hypertension (PH) is among the most severe complications of HIV infection. Only limited data are available on the efficacy of PH therapies in HIV-associated PH. Moreover, the potential impact of combination antiretroviral therapy on the progression of HIV-associated PH is still under investigation, and the effects of antiretroviral drugs on pulmonary hemodynamics remain controversial. Here, we show that 3 first-generation HIV protease inhibitors (ritonavir, amprenavir, and nelfinavir) partially protect against the development of hypoxia- or monocrotaline-induced PH in rats. The 3 drugs also partially reversed established PH in monocrotaline-treated rats, an effect associated with diminished pulmonary vascular remodeling due mainly to inhibition of smooth muscle hyperplasia. One suggested mechanism of this growth-inhibiting effect is inhibition of the Akt signaling pathway, which is a downstream target of growth factors such as platelet-derived growth factor and serotonin. These observations are consistent with a pharmacological effect of HIV protease inhibitors in humans because the HIV protease inhibitor doses used in our study animals were chosen on the basis of the plasma levels achieved in humans. Taken together, these results support the ability of HIV protease inhibitors to interfere with pulmonary vascular remodeling by inhibiting Akt phosphorylation and consequently pulmonary artery smooth muscle cell proliferation. Further studies are needed to assess the long-term effects of HIV protease inhibitors on PH progression in HIV-infected patients. See p 1937.

The Alternative Pathway Is Critical for Pathogenic Complement Activation in Endotoxin- and Diet-Induced Atherosclerosis in Low-Density Lipoprotein Receptor–Deficient Mice

Previous experiments in animals have suggested that the early components of the classical and lectin complement pathways may have protective effects against the development of atherosclerosis. In this study, we have addressed the role of the alternative pathway by crossing the low-density-lipoprotein receptor–deficient mouse model of atherosclerosis (Ldlr−/−) with mice that lack complement factor B (Bf−/−), the initiator of the alternative pathway. Under 2 different proatherogenic conditions, administration of lipopolysaccharide and high-fat diet, Bf−/−/Ldlr−/− mice showed markedly reduced atherosclerotic lesion formation compared with Ldlr−/− mice. The protective effects of factor B deficiency were associated with significant reductions in systemic and lesional complement activation. Overall, our data provide the first direct evidence of the proatherogenic role of the amplification of complement activation by the alternative pathway in response to lipopolysaccharide or high-fat diet. This work lends support for developing therapeutic strategies aiming to inhibit the complement system by blocking the alternative pathway without interfering with the protective effect(s) mediated by the classical and lectin pathways. See p 1948.
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