Cardiology Update

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Atherosclerosis causes coronary artery disease, myocardial infarction, stroke, and peripheral vascular disease.[1] Our understanding of pathogenesis of atherosclerosis continues to evolve: multiple factors are involved, including endothelial dysfunction,[2] dyslipidemia,[3] inflammation[4] and plaque rupture (**Figure 1**).[5] This underlies the importance of pleiotropic effects of statins in treating atherosclerosis.

In patients presenting with acute myocardial infarction, percutaneous coronary intervention with stenting reduces the rates of death and recurrent ischemia compared with medical therapy.[6] One significant advancement in treating acute myocardial infarction is the development of drug-eluting stents. Restenosis, which involves proliferation and migration of vascular smooth-muscle cells, was observed in patients with bare-metal stents. By coating stents with drugs that inhibits cell proliferation, restenosis is decreased significantly (**Figure 2**).[7]

In patients with coronary artery disease or survived myocardial infarction, the risk of sudden cardiac death is significant. About half a million people died of sudden cardiac death every year in US, and majority of them have underlying heart disease. In multiple large randomized clinical trials, implantable cardioverter-defibrillator saves lives in high risk patients (**Figure 3**).[8,9]

Implantable cardioverter-defibrillator saves lives, but patients still suffer from heart failure symptoms because of myocardial damage. An important development in treating heart failure is biventricular pacer/ICD. A significant amount of patients with heart failure also have interventricular conduction delay, resulting in dyssynchronous and ineffective contraction. By implanting a pacing lead inside the coronary sinus, synchronous and more effective contraction can be restored (**Figure 4**).[10]

Atrial fibrillation is the most common arrhythmia and its prevalence is increasing. It can lead to symptoms resulted from decreased cardiac output or stroke. Recent studies have demonstrated that in patients with paroxysmal atrial fibrillation, most triggers of atrial fibrillation are located inside the four pulmonary veins that connect to the left atrium. By isolating those veins electrically, atrial fibrillation can be cured in about 80% of patients (**Figure 5**).[11]

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Atherosclerotic Lesion in a Human Artery

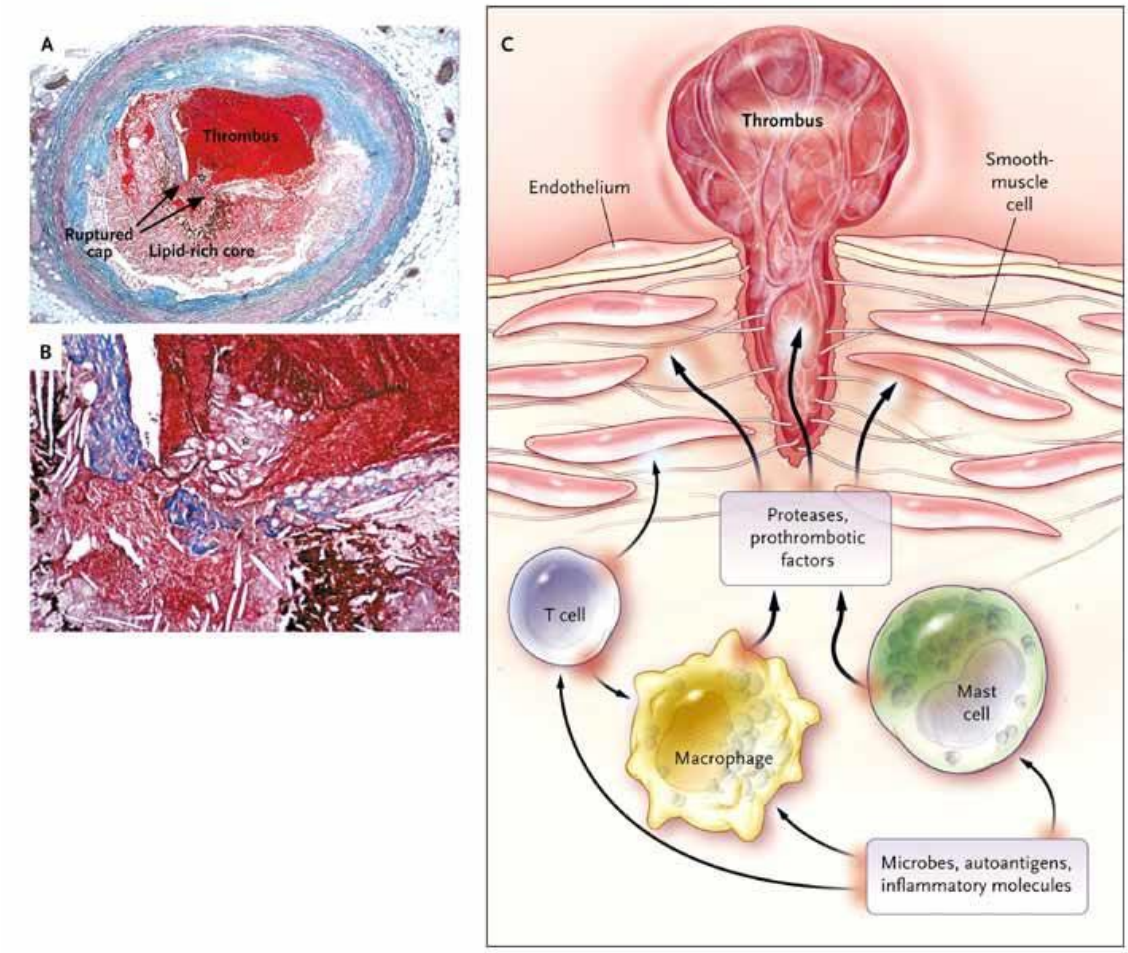

Figure 1. Atherosclerotic Lesion in a Human Artery. Panel A shows a cross-sectioned coronary artery from a patient who died of a massive myocardial infarction. It contains an occlusive thrombus superimposed on a lipid-rich atherosclerotic plaque. The fibrous cap covering the lipid-rich core has ruptured (area between the arrows), exposing the thrombogenic core to the blood. Trichrome stain was used, rendering luminal thrombus and intraplaque hemorrhage red and collagen blue. Panel B is a high-power micrograph of the area in Panel A indicated by the asterisk and shows that the contents of the atheromatous plaque have seeped through the gap in the cap into the lumen, suggesting that plaque rupture preceded thrombosis (the asterisk indicates cholesterol crystals). (Panels A and B courtesy of Dr. Erling Falk, University of Aarhus, Aarhus, Denmark.) Panel C illustrates the consequences of the activation of immune cells in a coronary plaque. Microbes, autoantigens, and various inflammatory molecules can activate T cells, macrophages, and mast cells, leading to the secretion of inflammatory cytokines (e.g., interferon-{gamma} and tumor necrosis factor) that reduce the stability of plaque. The activation of macrophages and mast cells also causes the release of metalloproteinases and cysteine proteases, which directly attack collagen and other components of the tissue matrix. These cells may also produce prothrombotic and procoagulant factors that directly precipitate the formation of thrombus at the site of plaque rupture.
(Adapted with permission from **Hansson G. N Engl J Med 2005; 352:1685-1695)**

The Development of Sirolimus from a Molecular Probe to Explore Cell-Cycle Regulation to an Inhibitor of Restenosis

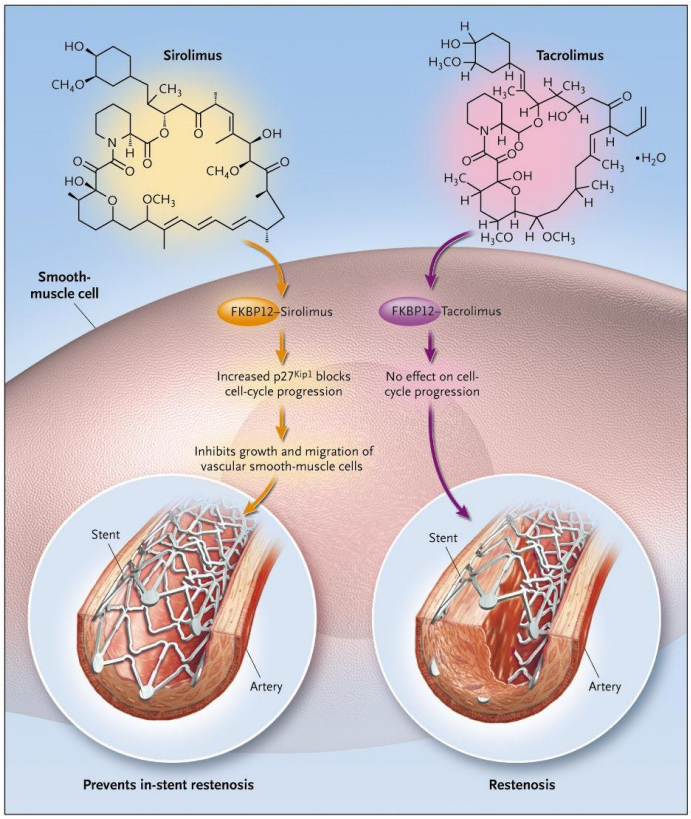

Figure 2. The Development of Sirolimus from a Molecular Probe to Explore Cell-Cycle Regulation to an Inhibitor of Restenosis. Sirolimus was initially used as a molecular probe to elucidate the fundamental pathways controlling the proliferation of vascular smooth-muscle cells. These studies revealed that sirolimus inhibits the growth and migration of vascular smooth-muscle cells in vitro (orange arrows). Sirolimus and the related immunosuppressant tacrolimus both bind to the same cystolic receptor FKBP12, but their actions are completely divergent: FKBP12-sirolimus inhibits the growth of vascular smooth-muscle cells, whereas FKBP12-tacrolimus does not (purple arrows). The mechanism by which sirolimus inhibits cell growth involves cell-cycle arrest at the transition from G1 to S. Sirolimus-resistant muscle cells were used to identify the important role of the cyclin-dependent kinase inhibitor p27Kip1 in mediating the antiproliferative and antimigratory activity of sirolimus. The identification of the key role of p27Kip1 in the ability of sirolimus to inhibit the proliferation and migration of vascular smooth-muscle cells in vitro was the basis for in vivo studies in a pig model of coronary-artery stenosis after balloon angioplasty. These in vivo studies demonstrated that sirolimus has a potent inhibitory effect on restenosis and provided the impetus to determine whether coating a coronary stent with sirolimus could inhibit in-stent restenosis.
(Adapted with permission from **Marks A. N Engl J Med 2003; 349:1307-1309**)

Diagram of a Single-Chamber Implantable Cardioverter-Defibrillator System

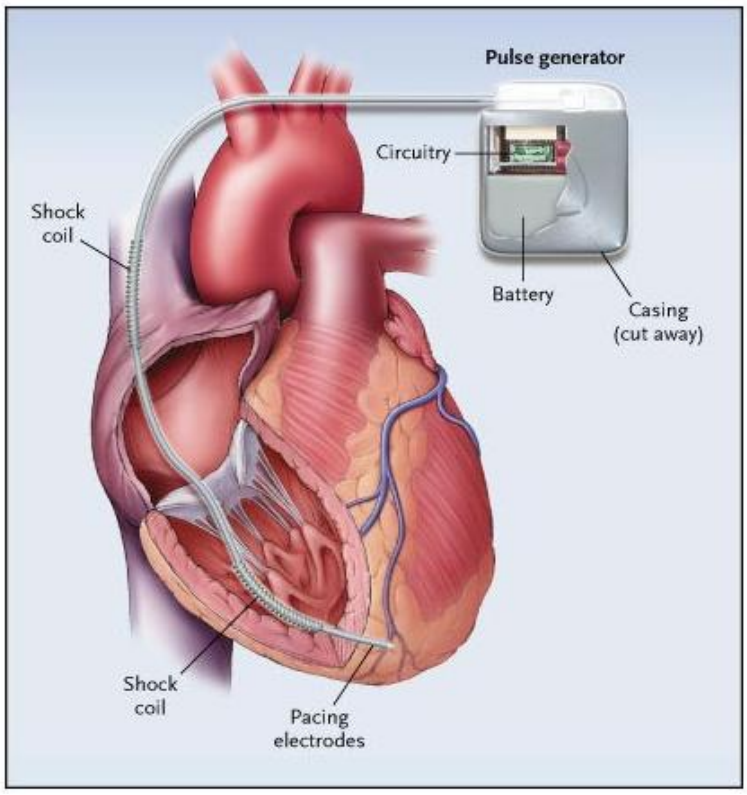

Figure 3. Diagram of a Single-Chamber Implantable Cardioverter-Defibrillator System. The pulse generator is usually placed in a subcutaneous pocket in the pectoral region. It contains a header with ports for leads, the battery and capacitors, memory chips, integrated circuits and microprocessors, and the telemetry module. The transvenous right ventricular lead contains the shock coils and pacing electrodes. Additional leads may be connected for right atrial or left ventricular pacing.
(Adapted with permission from **DiMarco J. N Engl J Med 2003; 349:1836-1847**)

The Cardiac Conduction System and Biventricular Pacing

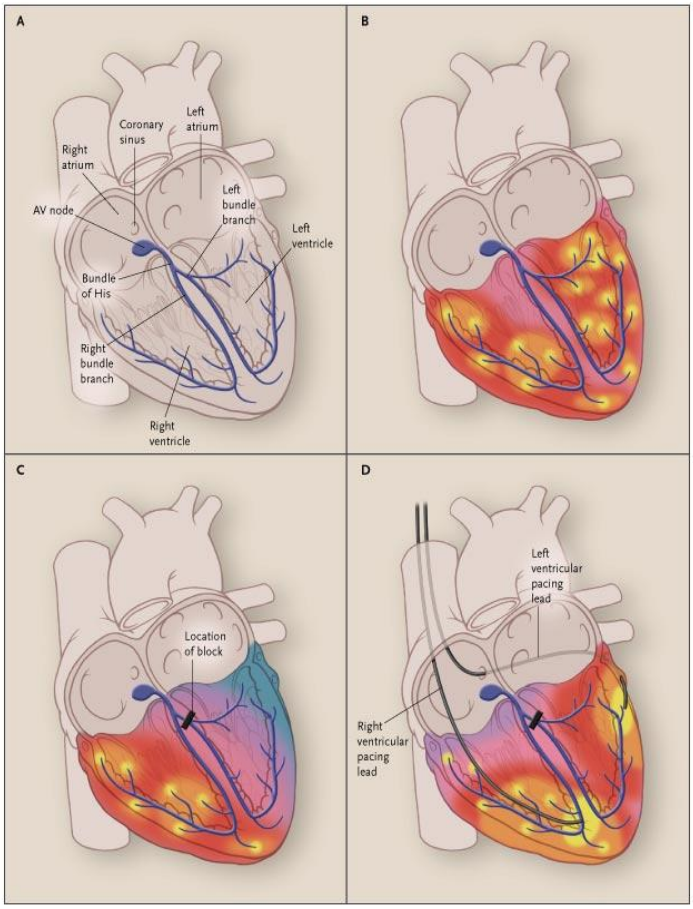

Figure 4. The Cardiac Conduction System and Biventricular Pacing. The cardiac conduction system is designed to initiate depolarization of the cardiac ventricles widely and synchronously. Panel A shows the anatomy of the system, with the locations of the atrioventricular (AV) node, the bundle of His, and the right and left bundle branches. With normal conduction, the left and right ventricles are depolarized simultaneously, with consequent simultaneous contraction (Panel B). In Panel B, yellow areas are the sites of earliest depolarization (at the terminal ramifications of the conduction system), with successive regions of depolarization shown in orange, red, and pink. In the setting of left bundle-branch block, the right ventricular free wall and the interventricular septum are depolarized rapidly (Panel C). There is a clinically significant delay in the depolarization of the left ventricular free wall. As a result, left ventricular contraction is dyssynchronous. In Panel C, the sites of earliest depolarization are yellow and are all in the right ventricle; successive regions of depolarization are shown in orange, red, pink, purple, and blue. With CRT, pacemaker leads are situated to stimulate both ventricles, thus bypassing the conduction block in the left bundle branch (Panel D). Simultaneous depolarization and simultaneous contraction of the ventricles is restored. In Panel D, the sites of early depolarizations are yellow and are near the tip of both pacemaker leads as well as in the branches of the normally conducting right bundle-branch system. Successive regions of depolarization are shown in orange, red, pink, and purple.
(Adapted with permission from **Jarcho J. N Engl J Med 2006; 355:288-294**)

Circumferential Pulmonary-Vein Ablation

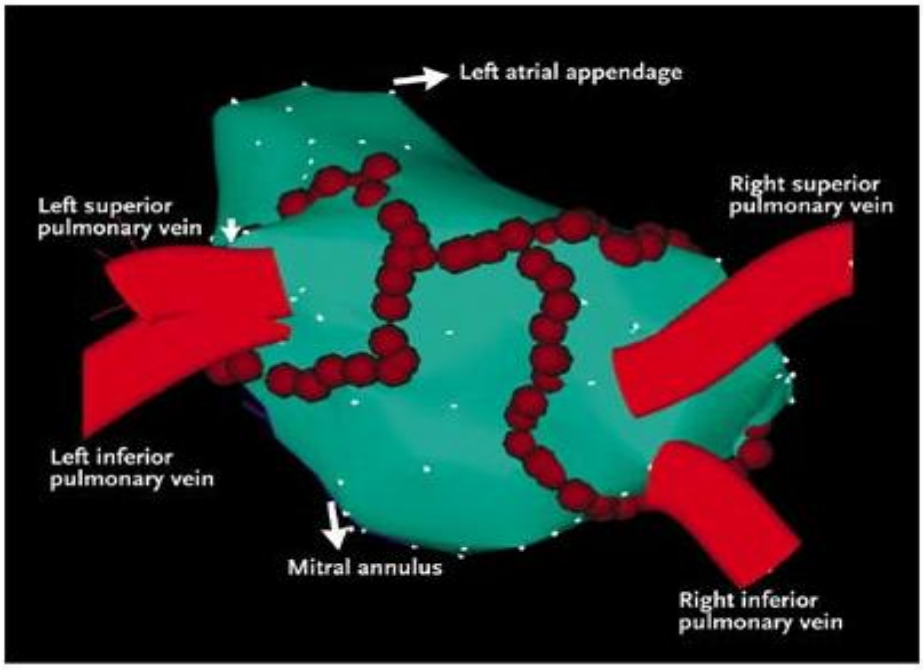

Figure 5. Circumferential Pulmonary-Vein Ablation. A three-dimensional electroanatomical depiction of the left atrium and the pulmonary veins is shown in a right posterior oblique projection with cranial angulation. The two encircling lesions were connected with an ablation line in the roof. Another ablation line was created along the mitral isthmus, between the left inferior pulmonary vein and the lateral mitral annulus.
(Adapted with permission from **Oral H et al. N Engl J Med 2006; 354:934-941**)