Augmentation of Left Ventricular Contractility by Cardiac Sympathetic Neural Stimulation

During worsening of congestive heart failure, an intrinsic counter-regulatory increase in humoral and neural sympathetic tone tries to compensate for the loss of ventricular contractility. This sympathetic hyperactivity might contribute to even more deterioration of heart failure. Antidiuretic pharmacological β-receptor blocker therapy has been shown to decrease mortality in heart failure but cannot be applied to all patients because of systemic side effects like arterial hypotension and bradyarrhythmia. On the other hand, in the end stage of acute heart failure, corrective treatment is often needed to override β-receptor downregulation and to immediately augment left ventricular contractility. However, this is not cardioselective in that it also affects systemic vascular tone, thereby increasing cardiac afterload and potentially diminishing peripheral organ perfusion. This study provides experimental evidence for the presence of sympathetic neural fibers alongside the coronary sinus that selectively innervate the left ventricle and can be electrically stimulated by transvenously introduced electrode catheters. Because the obtained increase in left ventricular contractility is not accompanied by tachycardia or an increase in peripheral vascular resistance, such an approach might reduce the likelihood of peripheral organ damage. On the other hand, ablation of the sympathetic nerves around the coronary sinus may be developed as a selective antidiuretic therapy in the last resort in patients with severe ventricular arrhythmias (eg, to stabilize patients) during an electrical storm. See p 1286.

Urinary Creatinine Excretion Rate and Mortality in Persons With Coronary Artery Disease: The Heart and Soul Study

Recent studies have demonstrated that low body mass index is associated with mortality in individuals with coronary artery disease, whereas higher body mass index is not. Lower body mass index may reflect low muscle mass rather than low fat. When serum creatinine is in steady state, urinary creatinine excretion rate is proportional to muscle mass. In 903 outpatients with stable coronary artery disease, we collected 24-hour urine collections and evaluated the relation of creatinine excretion rate with mortality over 6 years. Individuals within the lowest tertile of creatinine excretion rate were at >2-fold mortality risk compared with the highest tertile independently of body mass index, waist-to-hip ratio, traditional coronary artery disease risk factors, inflammatory biomarkers, and kidney function. Timed urine collection may provide an inexpensive and readily available method to measure muscle mass in outpatients with coronary artery disease and to garner additional information on mortality risk independently of conventional measures of body composition or traditional coronary artery disease risk factors. Future studies are required to determine whether resistive exercise and/or nutritional interventions can improve creatinine excretion rate and whether such improvements in creatinine excretion rate are associated with demonstrable improvements in health outcomes. See p 1295.

Parental Occurrence of Stroke and Risk of Stroke in Their Children: The Framingham Study

The Framingham Heart Study has prospectively verified data on the occurrence of stroke across 2 generations of participants, the original (parental) and offspring cohorts. We studied incident stroke risk among 3443 stroke-free offspring (53% female; mean age, 48 ± 14 years) with verified parental stroke status (by 65 years of age). Using multivariable Cox models adjusted for age, sex, sibship, and baseline stroke risk factors, we observed that over a period of 77 534 person-years, verified parental stroke by 65 years of age resulted in a nearly 3-fold increase in risk of offspring stroke (hazard ratio, 2.79; 95% confidence interval, 1.68 to 4.66; P < 0.001 for all stroke; and hazard ratio, 3.15; 95% confidence interval, 1.69 to 5.88; P < 0.001 for ischemic stroke). This was true for both maternal and paternal stroke. The increased risk persisted after adjustment for conventional stroke risk factors. Thus, parental stroke status might serve as a simple, clinically useful, aggregate measure of an individual’s hereditary propensity to stroke. It has been suggested that for many polygenic diseases and traits, testing for multiple risk alleles may not improve on the use of family history as a risk marker. See p 1304.

Heterogeneity of Genetic Modifiers Ensures Normal Cardiac Development

Individuals who share the same underlying basis for congenital heart disease can have presentations ranging from normal to life-threatening. Understanding the basis of such wide variability could suggest prognostic and therapeutic strategies focused not on the causes but on the modifiers of disease. We thus characterized the effect of genetic modifiers on the incidence of heart defects associated with mutation of the cardiac transcription factor Nkx2-5. Quantitative analyses of multiple inbred mouse strain crosses reveal the profound effect of polymorphic genetic modifiers. Protective and susceptibility alleles of modifier loci direct the manifestation of 1 or more types of heart defects, suggesting that they affect the sensitivity of specific cardiac developmental pathways to a perturbation. The modifiers alter the risk of a particular phenotype either independently or via epistatic interactions with other loci. The results intertwine the genetic basis of health and congenital heart disease, providing a conceptual framework to understand common clinical observations related to incomplete penetrance and pleiotropy. We propose that stabilizing selection generated a diverse set of polymorphisms so that in a genetically heterogeneous population the predominant effect of modifier genes is to ensure the robustness of cardiac development. See p 1313.

Recent Declines in Hospitalizations for Acute Myocardial Infarction for Medicare Fee-for-Service Beneficiaries: Progress and Continuing Challenges

Recent improvements in the prevention and treatment of cardiovascular disease should lead to decreased rates of acute myocardial infarction (AMI). However, the United States currently lacks a national surveillance system for assessing the incidence of AMI, and community-based studies are somewhat conflicting. A contemporary national evaluation of AMI rates is needed to determine whether AMI rates have decreased across demographic groups. Using administrative data from a national sample of Medicare fee-for-service beneficiaries from 2002 to 2007, we found that rate of hospitalizations with a principal discharge diagnosis of AMI declined from 1131 to 866 per 100,000 beneficiary-years, a relative decline of 23.4%. The AMI hospitalization rate fell faster than hospitalizations for all diagnoses other than AMI. Elderly black men and women had
smaller declines in AMI hospitalization rates compared with white men and women. Our findings suggest that AMI incidence has decreased substantially for elderly Americans during this time, but additional research is required to evaluate why the declines appears slower for black patients compared with white patients. See p 1322.

**Modeled Economic Evaluation of Alternative Strategies to Reduce Sudden Cardiac Death Among Children Treated for Attention Deficit/Hyperactivity Disorder**

Stimulants are commonly used to treat children with attention deficit/hyperactivity disorder. These drugs have adrenergic properties and may increase the risk for sudden cardiac death in individuals with cardiac abnormalities such as cardiomyopathies or conduction defects. Although the possible value of routine ECG screening before stimulant treatment is an object of debate, current clinical guidelines recommend medical history taking and physical examination, with ECG and cardiology evaluation only for the children who screen positive on history taking and physical examination. In the first such study, we conducted a modeled economic evaluation of 3 different approaches to screening children for possible cardiac abnormalities before stimulant treatment. The analyses indicate that adding ECG to history taking and physical examination would prevent sudden cardiac death at an estimated cost of about $39,000 per quality-adjusted life-year. Because of the low sensitivity and specificity of history taking and physical examination, relying exclusively on an ECG screening would lead to the more favorable cost of about $27,000 per quality-adjusted life-year. Monte Carlo simulations suggest that screening with ECG has borderline cost-effectiveness according to generally accepted willingness-to-pay criteria. These analyses provide useful estimates that contribute to the current debate on the possible role of ECG for preventing sudden cardiac death in childhood. See p 1329.

**Complement Regulator CD59 Protects Against Angiotensin II–Induced Abdominal Aortic Aneurysms in Mice**

Aneurysm, including abdominal aortic aneurysm (AAA), is considered an immune and inflammatory disease. Complement is a main effector of the immune response and inflammation. However, the role of complement in the aneurysm pathogenesis has not been extensively investigated. The complement system is activated by 3 activation cascades, which lead to formation of the membrane attack complex (MAC). MAC, a macromolecular pore capable of inserting itself into cell membranes and lysing heterologous cells and bacteria, is an important mediator of cellular signals, including nuclear factor-κB and activator protein-1, which trigger mitogenic effects. To protect autologous cells from MAC, an array of complement regulators, including CD59, have evolved to restrict complement activation. CD59 strongly restricts MAC formation. Here, we demonstrated that in the angiotensin-induced abdominal aortic aneurysm model, deficiency of CD59 in ApoE-null mice accelerated the abdominal aortic aneurysm development, whereas transgenic over-expression of CD59 attenuated the abdominal aortic aneurysm progression. The severity of aneurysm positively correlates with C9 deposition, the activities of matrix metalloproteinase-2 and -9, and the levels of phosphorylated c-Jun, c-Fos, IKK-α/β, and p65. Furthermore, we demonstrated that MAC directly induced gene expression of matrix metalloproteinase-2 and -9 in vitro, which depended on the activation of the activator protein-1 and nuclear factor-κB signaling pathways. Together, these results shed light on the important pathogenic role of MAC in aneurysm, point toward the molecular mechanism of MAC-activated signaling pathways in aneurysm, and suggest that inhibition of MAC may provide a novel approach for the treatment/prevention of aneurysm. See p 1338.

**Adipocyte Modulation of High-Density Lipoprotein Cholesterol**

Adipose tissue harbors a major pool of free cholesterol, but its role in regulating circulating high-density lipoprotein (HDL) cholesterol is poorly understood. In this work, we present the first evidence that adipocytes transfer cholesterol to HDL in vivo as well as in vitro. We identified a differentiation-dependent role for the lipid transporters ATP-binding cassette subfamily A member 1 and scavenger receptor class B type I, but not ATP-binding cassette subfamily G member 1, in adipocyte cholesterol efflux to apolipoprotein A-I and mature HDL, respectively. We also provide experimental evidence that both ATP-binding cassette subfamily A member 1 and scavenger receptor class B type I can regulate adipocyte cholesterol transfer to HDL in vivo. Finally, we show that adipocyte inflammation downregulates transporters and impairs adipocyte cholesterol efflux to HDL. Our findings suggest a role for mature adipose in directly maintaining HDL cholesterol levels. Conversely, adipose inflammation may attenuate adipocyte lipiddation of HDL and may directly contribute to lower HDL cholesterol in adipose inflammatory states such as obesity and type 2 diabetes mellitus. Thus, adipose tissue cholesterol homeostasis may be a direct therapeutic target for modulation of HDL levels in vivo. See p 1347.