Cardiac Sodium Channel Gene Variants and Sudden Cardiac Death in Women

Our present ability to identify individuals who are at risk for sudden cardiac death (SCD) in the general population is poor. Although SCD risk has a heritable component, our understanding of the genetic basis of SCD is most advanced in rare arrhythmic disorders such as the long-QT and Brugada syndromes, in which mutations in genes encoding cardiac ion channels result in increased susceptibility for SCD. The extent to which the heritable component of more common forms of SCD might be due to similar mutations or rare polymorphisms in these same genes is currently unknown. To address this question, we determined both the prevalence and function of mutations and rare coding sequence variants in 5 cardiac ion channel genes among 113 unselected cases of SCD drawn from 2 large prospective cohorts of women and men. No mutations or rare variants were identified in any of the 53 subjects who were men. In contrast, 2 mutations and 3 rare missense variants in a single ion channel gene, the cardiac sodium channel SCN5A, were found in 6 of 60 women (10%), and all 1 resulted in significantly shorter recovery times from channel inactivation. The overall frequency of these rare variants in SCN5A was significantly higher in the SCD cases (6/60, 10.0%) compared with controls (12/733, 1.6%; P = 0.001) from the same population. These data suggest that functionally significant rare variants in SCN5A may contribute to SCD risk in the general population and particularly among women. See p 16.

Effects of Angiotensin-Converting Enzyme Inhibition in Low-Risk Patients Early After Coronary Artery Bypass Surgery

The Ischemia Management with Accupril post-bypass Graft via Inhibition of the coNverting Enzyme (IMAGINE) study suggests that although angiotensin-converting enzyme (ACE) inhibitors are useful in the therapy of patients with coronary artery disease, it would appear that in patients with preserved left ventricular function (ejection fraction >40%) and without a clear indication for an ACE inhibitor (uncontrolled hypertension, diabetes with microalbuminuria or insulin dependency), early (≤7 days after coronary artery bypass grafting) initiation of an ACE inhibitor is not beneficial and may even increase the incidence of adverse events over the early (3 months) postoperative period. Indeed, the results of the IMAGINE study suggest that in such low-risk patients, it may be wise to delay the initiation of an ACE inhibitor beyond 7 days after coronary artery bypass grafting unless a specific indication other than the presence of coronary artery disease exists. The results of IMAGINE also suggest that if early initiation of an ACE inhibitor after coronary artery bypass grafting is indicated, it should be done with care. Finally, the results of the IMAGINE study do not modify the present recommendations for the use of ACE inhibitors in stable patients with coronary artery disease; however, owing to the very low event rate in IMAGINE-like patients, the absolute benefits of ACE inhibitors, if any, would be so small that individualized therapy, depending on the patient’s associated risk factors, is recommended. See p 24.

Utility of Currently Recommended Pediatric Dyslipidemia Classifications in Predicting Dyslipidemia in Adulthood: Evidence From the Childhood Determinants of Adult Health (CDAH) Study, Cardiovascular Risk in Young Finns Study, and Bogalusa Heart Study

Good prospective evidence exists that children and adolescents with abnormal lipid and lipoprotein levels are not only at risk of becoming adults with abnormal levels but that exposure to adverse levels in early life may induce arterial changes that facilitate atherosclerosis. Because of this evidence, there has been a resurgent interest in screening children and adolescents for dyslipidemias to identify those at high risk for cardiovascular disease later in life and those who may benefit from early intervention. Although 2 groups (the National Cholesterol Education Program and Jolliffe and Janssen [Circulation. 2006;114:1056–1062]) have proposed pediatric cut points for normal-, borderline-, and high-risk lipoprotein variable levels, no study has assessed which of these classifications is most effective for predicting those adolescents who will develop abnormal levels in adulthood. On the basis of pooled data from 3 prospective cohort studies from Australia, Finland, and the United States, our results suggest that clinicians wishing to identify lipid disorders in adolescents would likely improve risk stratification by the separate adoption of cut points for high-density lipoprotein cholesterol signalized by Jolliffe and Janssen and National Cholesterol Education Program–stipulated cut points for total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Our data also suggest that clinicians employing current pediatric guidelines for targeted lipoprotein screening in children and adolescents with a positive family history of premature coronary heart disease or who are overweight or obese need to consider that a substantial number of those adolescents identified with high total cholesterol or low-density lipoprotein cholesterol levels will not have high-risk levels in early adulthood and that most individuals who develop abnormal high-density lipoprotein cholesterol or triglyceride levels as adults will not be identified in adolescence. See p 32.

Diastolic Stiffness of the Failing Diabetic Heart: Importance of Fibrosis, Advanced Glycation End Products, and Myocyte Resting Tension

Mortality among diabetic patients with heart failure is high. Diabetes mellitus–related metabolic disturbances contribute importantly to their myocardial dysfunction. Increased diastolic left ventricular (LV) stiffness is an early manifestation of myocardial dysfunction and frequently becomes an important functional deficit, because many diabetic patients present with heart failure and normal LV ejection fraction. Excessive diastolic LV stiffness of the diabetic heart is usually attributed to myocardial fibrosis or to myocardial deposition of advanced glycation end products. Hypertrophied cardiomyocytes isolated from LV biopsy samples of heart failure patients with normal LV ejection fraction have a high resting tension, which correlates with greater in vivo diastolic LV stiffness. This increased resting tension could be an important contributor to the increased diastolic LV stiffness of the diabetic heart. With the use of LV endomyocardial biopsy samples, the present study assessed myocardial fibrosis, myocardial advanced glycation end product deposition, and resting tension of isolated cardiomyocytes in diabetic
patients with heart failure and either normal or reduced LV ejection fraction. All patients were free of coronary artery disease and had an elevated diastolic LV stiffness. The mechanisms responsible for the elevated diastolic LV stiffness differed between heart failure patients with normal and reduced LV ejection fraction. Myocardial deposition of collagen and advanced glycation end products was more important in patients with reduced ejection fraction, whereas a high cardiomyocyte resting tension was more important in patients with normal ejection fraction. These mechanistic studies suggest that correction of high cardiomyocyte resting tension, possibly through regression of cardiomyocyte hypertrophy, may be an important therapeutic target for diabetic patients with heart failure and normal ejection fraction. See p 43.

**Platelet Sarcoplasmic Endoplasmic Reticulum Ca$$^{2+}$$-ATPase and $$\mu$$-Calpain Activity Are Altered in Type 2 Diabetes Mellitus and Restored by Rosiglitazone**

Diabetes mellitus, a major risk factor for vascular diseases, is associated with accelerated atherosclerosis and a high rate of arterial thrombotic complications. We found that platelets from patients with type 2 diabetes mellitus that display hyperaggregability to thrombin also manifest enhanced tyrosine nitration and inactivation of the sarcoplasmic endoplasmic reticulum Ca$$^{2+}$$-ATPase, elevated platelet [Ca$$^{2+}$$], and activation of $$\mu$$-calpain. One consequence of this cascade of events was that platelet endothelial cell adhesion molecule-1 was identified as a $$\mu$$-calpain substrate, and its in vitro degradation was stimulated by peroxynitrite and prevented by calpain inhibitors. Calpain activation also was linked to hyperresponsiveness to thrombin and the loss of platelet sensitivity to nitric oxide synthase inhibitors. Moreover, platelets from patients with type 2 diabetes mellitus (hemoglobin A$$\text{1c}$$ >6.6%) contained little or no intact platelet endothelial cell adhesion molecule-1, whereas degradation products were detectable. These changes could be largely reversed by treating diabetic patients with the peroxisome proliferator–activator-$$\gamma$$ agonist rosiglitazone (8 mg/d for 12 weeks). Although heated debate currently exists with respect to rosiglitazone and the treatment of cardiovascular disease, it seems that megakaryocytes/platelets are additional cellular targets for peroxisome proliferator–activated receptor-$$\gamma$$ agonists and that there may be a beneficial effect of rosiglitazone therapy on platelet function. See p 52.

**Adenyl Cyclase Type 6 Deletion Decreases Left Ventricular Function via Impaired Calcium Handling**

Adenyl cyclase (AC) content and function govern $$\beta$$-adrenergic receptor response and left ventricular contractility and therefore are of clinical interest. A fundamental understanding of the biochemical and physiological roles of AC is an indispensable first step in the development of new treatments for heart diseases. The specific roles and relative importance of AC6 versus AC5, the 2 AC types most abundantly expressed in cardiac myocytes, are unknown. Current understanding of the role of AC6 in cardiac function comes solely from gain-of-function models. To see directly the importance of AC6 in cardiac physiology and $$\beta$$-adrenergic receptor signaling, we generated mutant mice in which AC6 was absent. Deletion of AC6 has striking negative effects on the heart, effects that reverberate from the cellular to the organ level and include impairments in calcium handling, left ventricular force generation, and contractile responsiveness. These alterations are qualitatively and quantitatively different from those seen with AC5 deletion, which indicates that these 2 AC isoforms, which share substantial sequence homology, fulfill different biological roles. These results suggest that maintenance of AC6 content and function may be a rational therapeutic goal in heart failure, in which calcium handling, left ventricular force generation, and contractile responsiveness are impaired. See p 61.

**C1-Esterase Inhibitor Protects Against Neointima Formation After Arterial Injury in Atherosclerosis-Prone Mice**

Human C1-esterase inhibitor (C1-inhibitor) is available in clinical practice for substitution therapy of hereditary angioedema. Many observations suggest that C1-inhibitor is a multifaceted antiinflammatory protein that exerts its effects through a variety of mechanisms. Notably, treatment with C1-inhibitor has also been implied to be beneficial in a variety of disease models, including sepsis, ischemia-reperfusion injury, acute transplant rejection, traumatic shock, and vascular leakage syndromes after interleukin-2 therapy or cardiopulmonary bypass. The expected beneficial effect has been attributed primarily to an inhibition of the complement and contact system and several different noncovalent interactions that are unrelated to protease inhibition. The direct interactions of C1-inhibitor with selectins result in suppression of leukocyte rolling and transmigration across the endothelial surface. Furthermore, some data suggest a beneficial effect in human inflammatory disease. In the present study, C1-inhibitor successfully limited neointimal hyperplasia and inflammation after arterial injury by direct effects on the complement system but also by directly blocking the leukocyte–endothelial cell interaction. These data provide a rationale for the potential use of C1-inhibitor in clinical practice for conditions in which endothelial activation and complement and contact system activation promote pathogenesis and disease progression. A very recent study has shown that low C1-inhibitor levels are associated with and are predictive of early restenosis after carotid endarterectomy in humans. Therefore, it is conceivable that C1-inhibitor may be useful in the prevention of restenosis in patients with atherosclerosis after arterial interventions such as percutaneous coronary angioplasty or stent implantation. See p 70.

**New-Onset Heart Failure Due to Heart Muscle Disease in Childhood: A Prospective Study in the United Kingdom and Ireland**

This first national, prospective study of new-onset heart failure due to heart muscle disease requiring hospitalization in children has shown an overall incidence of 0.87/100 000 and an incidence of dilated cardiomyopathy (due to all causes, including myocarditis) of 0.76/100 000. This appears remarkably similar to data from Australia and the United States. Our multivariable analysis of the survival data is at variance with some earlier work and indicates a better outcome for younger children and for those with better systolic function at presentation. Overall, one third of children died or required transplantation within 1 year of presentation. See p 79.

**Long-Term Survival, Modes of Death, and Predictors of Mortality in Patients With Fontan Surgery**

The univentricular heart encompasses a spectrum of rare congenital cardiac defects often ultimately managed by a Fontan procedure, which diverts systemic venous return to the pulmonary artery. As patients survive into adulthood, it is increasingly pertinent to define modes and predictors of death. In a database registry of patients born in 1985 or earlier with Fontan surgery and follow-up at Children’s Hospital Boston, 261 patients were followed up for 12.2 years; of them, 76 (29.1%) died, 5 (1.9%) received transplants, 5 (1.9%) had Fontan revision, and 21 (8.0%) had Fontan conversion. Not unex-
pectedly, perioperative mortality decreased steadily over time and accounted for 68.4% of all deaths. Gradual attrition was noted thereafter, predominantly from thromboembolic, heart failure–related, and sudden deaths. In perioperative survivors, 90% freedom from all-cause death or transplantation was observed at 10 years, 83% at 20 years, and 70% at 25 years. Risk of death from thromboembolism increased 15 years after Fontan surgery and was predicted by clinically identified thrombus and lack of aspirin or warfarin therapy. Heart failure mortality was minimal the first 10 years. Independent risk factors were single right ventricular morphology, higher postoperative right atrial pressure, and protein-losing enteropathy. The incidence of sudden death was 0.15% per year, with most events of presumed arrhythmic origin. Therefore, this analysis extends our knowledge of long-term outcomes in the first adult cohort of patients with Fontan surgery by elucidating modes of death, time-dependent patterns, and risk factors for each subtype. See p 85.

**Cardiovascular Risk Factors and Venous Thromboembolism: A Meta-Analysis**

Venous thromboembolism and atherosclerotic cardiovascular disease are commonly considered 2 distinct entities with different predisposing risk factors. However, recent studies have suggested that patients with venous thromboembolism may be at increased risk of both asymptomatic and symptomatic atherosclerosis; other studies also have suggested a potential association between major cardiovascular risk factors and venous thrombosis. We have performed a systematic review of the literature and a meta-analysis to assess the strength of the evidence supporting such an association. The results of our study clearly support the hypothesis that major risk factors for atherothrombotic disease also are significantly associated with venous thromboembolism. In particular, we have found a statistically significant association between venous thromboembolism and obesity, diabetes mellitus, low high-density lipoprotein cholesterol, high triglycerides, and arterial hypertension. Although the estimated odds ratios for these variables were less robust than those reported for established major risk factors for venous thrombosis such as cancer or surgery, our findings are clinically relevant because cardiovascular risk factors are more common and often coexist, and as is well known for atherosclerotic disorders, their coexistence is associated with an additive causative effect. The results of our study may open new perspectives in the management of patients with venous thromboembolism, in particular for those patients presenting with an apparently unprovoked event. Recognition of cardiovascular risk factors, if confirmed to be relevant for venous thrombosis, may support new strategies for both primary and secondary prevention. In particular, the role of weight loss and antiplatelet and lipid-lowering therapy needs to be specifically assessed. See p 93.