Mobile Thrombus on Device Leads in Patients Undergoing Ablation: Identification, Incidence, Location, and Association With Increased Pulmonary Artery Systolic Pressure

This article describes the frequent (30% of patients) presence of sizable mobile thrombus on pacemaker and defibrillator leads identified with careful intracardiac echocardiographic assessment during ablation procedures for atrial fibrillation and ventricular tachycardia. These thrombi were more frequently seen on the atrial portion of the leads. Prior use of oral anticoagulants or antiplatelet agents, the number and age of leads, and presence of a superior vena cava coil were not specifically associated with lead thrombi during the procedure. The group with thrombus had a higher pulmonary artery pressure, suggesting the possibility that patients with lead thrombi may have subclinical pulmonary emboli elevating the pressure and/or that higher pulmonary artery pressure predisposes to thrombus formation in right-sided cardiac chambers. Further study is warranted to identify hematologic or other clinical factors that may increase patients’ risk of forming device lead thrombi and to assess the potential clinical impact of these thrombi. See p 772.

Coronary Artery Wall Shear Stress Is Associated With Progression and Transformation of Atherosclerotic Plaque and Arterial Remodeling in Patients With Coronary Artery Disease

Atherosclerosis progression in human coronary arteries is modulated by the interplay of systemic risk factors and local hemodynamic forces, including wall shear stress (WSS). Cell culture and experimental animal models have shown that endothelium exposed to low WSS displays an atherosclerotic phenotype with focal development of atherosclerosis and vascular remodeling. Using a comprehensive in vivo method of WSS assessment, we prospectively studied serial changes in coronary plaque area and composition and in arterial remodeling with radiofrequency backscatter intravascular ultrasound in segments with low, intermediate, and high WSS in patients with nonobstructive coronary artery disease. The findings of this study demonstrate that low coronary WSS is associated with plaque progression and constrictive remodeling and that high WSS is associated with plaque regression, expansive remodeling, and transformation of plaque composition to a more vulnerable phenotype. These data add to our understanding of the relationship between WSS, intravascular ultrasound–defined plaque burden and composition, and vascular remodeling in patients with coronary artery disease. In addition, combining such in vivo hemodynamic profiling with anatomic evaluation of vascular remodeling, plaque burden and composition, cap thickness, and plaque deformation may be incremental in prediction of plaque progression and transformation. In concert with systemic risk stratification, multimodality imaging can potentially identify focal coronary segments at high risk for future coronary events that could be approached by intensified regional or systemic therapies to alter the hemodynamic environment and subsequent pathobiological consequences. See p 779.

Dose Response Between Physical Activity and Risk of Coronary Heart Disease: A Meta-Analysis

Physical activity has clearly been shown to decrease the risk of developing coronary heart disease. However, the dose-response relation (How much activity is needed? What level of risk reduction is associated with specified levels of activity? Does the risk continue to decrease at higher levels of activity?) is less clear. This is the first meta-analysis of epidemiological studies to quantify the dose-response relation, examining both the specific amounts of physical activity and associated risk reductions for coronary heart disease (Previous meta-analyses have quantified only risk reductions, not the specific doses of activity required). We found that individuals who engaged in the equivalent of 150 min/wk of moderate-intensity leisure-time physical activity (corresponding to the minimum amount recommended by the 2008 US federal guidelines) had a 14% lower coronary heart disease risk compared with those reporting no leisure-time physical activity. Those engaging in the equivalent of 300 min/wk of moderate-intensity leisure-time activity had a 20% lower risk. At higher levels of physical activity, relative risks were modestly lower; eg, at 5 times the minimum recommended, there was a 25% lower risk. Persons who were physically active at levels lower than the minimum recommended amount also had a significantly lower risk of coronary heart disease. These findings provide quantitative data that support the 2008 US physical activity guidelines. They indicate that the biggest bang for the buck for coronary heart disease risk reduction occurs at the lower end of the activity spectrum: very modest, achievable levels of physical activity. See p 789.

Critical Role for Stromal Interaction Molecule 1 in Cardiac Hypertrophy

The cardiac muscle responds to mechanical and humoral stress by hypertrophic growth of individual myocytes. Although some degree of cardiac hypertrophy serves to reduce wall stress and helps to compensate for increased load on the myocardium, sustained prohypertrophic signaling within cardiomyocytes is clearly detrimental and a major factor contributing to the progression to failure. The activation of Ca2+-dependent signaling pathways has been identified as critical for cardiac hypertrophy. However, it has remained largely unclear how Ca2+ triggers signaling in cardiac myocytes in the presence of the rapid and large Ca2+ fluctuations that occur during excitation contraction coupling. Here, we have studied the role of stromal interaction molecule 1 in cardiomyocytes, a molecule that has been described in several cell types as critical for Ca2+ entry. By manipulating its expression, we found stromal interaction molecule 1 to be both sufficient and necessary for cardiomyocyte hypertrophy in vitro and in the adult heart in vivo. Stim1 silencing by viral gene transfer protected rats from pressure overload–induced cardiac hypertrophy. These data demonstrate an important role for stromal interaction molecule 1 in cardiac hypertrophy and may lead to the development of novel approaches to prevent cardiac dysfunction. See p 796.

Mitochondrial Transporter ATP Binding Cassette Mitochondrial Erythroid Is a Novel Gene Required for Cardiac Recovery After Ischemia/Reperfusion

This study reports that the mitochondrial transporter ATP binding cassette mitochondrial erythroid (ABC-me; ABCB10) plays an essential role in the recovery of cardiac function after ischemia/reperfusion. This is demonstrated by the impaired recovery of hemodynamic function (reduced by half) after ischemia/reperfusion in mice having inactivation of 1 allele of ABC-me (ABC-me+/−). Hemodynamic dysfunction was due to abnormalities in diastolic pressure and contraction, both of which are energy dependent (in the
form of ATP) and thus reliant on normal mitochondrial bioenergetics. In this regard, ABC-me inactivation caused increased oxidative damage to mitochondria, which decreased their ability to synthesize ATP. In addition, sarcoplasmic reticulum calcium ATPase was also damaged by oxidation, contributing to the diastolic dysfunction observed in ABC-me<sup>−/−</sup> hearts after ischemia/reperfusion. Thus, decreased protection from oxidative damage induced by ischemia/reperfusion causes the impaired recovery of hemodynamic function in ABC-me<sup>−/−</sup> hearts. This is further demonstrated by the restoration of all the defects described in ABC-me<sup>−/−</sup> hearts by an antioxidant pretreatment with a superoxide dismutase/catalase mimetic (EUK-207). The potential clinical relevance of these findings is emphasized by 2 different aspects: ABC-me is a transporter and might be subject to competitive inhibition by drugs, and genetic variations (mutations/polymorphisms in the gene or the promoter) partially inactivating ABC-me may determine the ability of an individual to tolerate ischemia/reperfusion. These aspects are of potential clinical relevance because they could predict the outcome from ischemia/reperfusion or determine selection of the appropriate treatment of individuals harboring a partial inactivation. See p 806.

**Competing Risks for Death and Cardiac Transplantation in Children With Dilated Cardiomyopathy: Results From the Pediatric Cardiomyopathy Registry**

Prior studies of outcomes for children with dilated cardiomyopathy (DCM) have used a composite end point of death and cardiac transplantation and may have missed identifying predictive factors differentially affecting outcomes, which affect the transplantation listing process. Using competing risk analysis, this study found that at the time of DCM diagnosis, the presence of congestive heart failure, echocardiographic evidence of more severe disease, and increased age at diagnosis predicted worse outcomes, with certain key differences between etiologic groups. For children with idiopathic disease, diagnosis after 6 years of age, congestive heart failure, decreased left ventricular (LV) fractional shortening, increased LV end-diastolic dimension, and decreased height-for-age scores who might require more urgent consideration for transplantation listing. For children with neuromuscular disease, decreased LV fractional shortening predicted death or transplantation, whereas increased LV dilation was predictive of use of transplantation but not of mortality in idiopathic DCM, calling into question the importance of this factor in the decision to list for transplantation. Routine height measurement could highlight those with idiopathic DCM and lower height-for-age z scores who might require more urgent consideration for transplantation listing. For children with myocarditis, older age at diagnosis, congestive heart failure, and increased LV end-diastolic dimension predicted transplantation but not death. For children with myocarditis, older age at diagnosis, congestive heart failure, and increased LV end-diastolic dimension predicted death or transplantation. These results suggest that the etiology of DCM modifies the importance of particular predictive factors. The ability to predict failed medical management may improve if the etiology of the cardiomyopathy can be established earlier. Additionally, analyses of registry data in this manner allow the postulation of predictive algorithms of clinical outcomes. See p 814.

**Bleeding Risk in Very Old Patients on Vitamin K Antagonist Treatment: Results of a Prospective Collaborative Study on Elderly Patients Followed by Italian Centres for Anticoagulation**

Vitamin K antagonists therapy is increasingly being used for the secondary prevention of venous thromboembolism and the prevention of stroke in atrial fibrillation. Bleeds are the major concern for vitamin K antagonist prescription, especially in very old patients who carry many risk factors for bleeding. We aimed to assess the incidence and risk factors for bleedings in patients who started on vitamin K antagonist at ≥80 years of age. The observed rate of major bleeding was acceptably low, notwithstanding the particularly advanced age of the patients. This could be explained at least in part by the good quality of the international normalized ratio control obtained in this cohort of patients, who were managed in experienced centers. We confirmed that the first 3 months of treatment carry the highest risk of bleeding, and we found a lower risk of bleeding in atrial fibrillation compared with venous thromboembolism patients. The presence of renal failure was significantly associated with bleeding risk. This is particularly important given that more than half had moderate renal failure, suggesting the need for careful monitoring of renal function over time, especially when the new anticoagulant drugs with a prevalent renal route of excretion are introduced. Bleeding risk was also significantly associated with history of previous bleeding events, previous falls, and cancer. This large study suggests that age in itself should not be considered a contraindication to vitamin K antagonist treatment. An adequate management of this therapy with careful monitoring of patients in specifically trained centers allows very old and frail patients to benefit from vitamin K antagonist thromboprophylaxis. See p 824.

**Involvement of Endoplasmic Stress Protein C/EBP Homologous Protein in Arteriosclerosis Acceleration With Augmented Biological Stress Responses**

Complex interactions among numerous biological pathways are implicated in the pathogenesis of arteriosclerosis such as atherosclerosis and vascular remodeling. In particular, responses to inflammation and oxidative stress have been considered to play central roles in arteriosclerosis development. In addition, recent studies revealed endoplasmic reticulum stress to be associated with atherosclerosis involving free cholesterol–induced macrophage apoptosis. However, details of the molecular mechanisms of interactions among classic atherogenic actions and endoplasmic reticulum stress responses remained to be elucidated. This study focused on the transcription factor C/EBP homologous protein (CHOP), which is well known to be induced by endoplasmic reticulum stress, mediating apoptotic cell death. Here, using CHOP-deficient mice, we show that CHOP plays important roles in accelerating 2 types of arteriosclerosis: cuff injury–induced neointimal formation and hypercholesterolemia-induced atherosclerosis. Augmented inflammatory and oxidative stress responses mediated by CHOP are important underlying mechanisms. Furthermore, CHOP, especially that expressed in hematopoietic and vascular cells, is involved in inflammatory interactions among macrophages, endothelial cells, and vascular smooth muscle cells, acting in a coordinated fashion to promote arteriosclerosis development. Thus, these observations of this noncanonical role of CHOP may lead to a better understanding of the molecular pathogenesis of vascular remodeling and atherosclerosis. Furthermore, given that neointimal formation is an important feature of postangioplasty restenosis of human coronary arteries, this study provides potential strategies for the prevention of cardiovascular diseases and the advancement of coronary intervention therapies. See p 830.