Paradoxical Effect of Increased Diastolic Ca\(^{2+}\) Release and Decreased Sinoatrial Node Activity in a Mouse Model of Catecholaminergic Polymorphic Ventricular Tachycardia

Catecholaminergic polymorphic ventricular tachycardia is a congenital arrhythmogenic disease linked to \(\beta\)-adrenergic–induced ventricular arrhythmias that has a high mortality in children and young adults when untreated. As common features of the catecholaminergic polymorphic ventricular tachycardia phenotype, supraventricular arrhythmias have also been described in catecholaminergic polymorphic ventricular tachycardia patients. The reason why ventricular myocytes exhibit stress-induced hyperactivity (ventricular ectopies and tachycardia) whereas sinoatrial node is often hypoxic (sinus bradycardia) remains elusive. Here, we explored for the first time \([\text{Ca}^{2+}]\) activity of sinoatrial node cells in intact tissues obtained from a mouse bearing the RyR2\^{R4496C}\ catecholaminergic polymorphic ventricular tachycardia mutation. Our results indicate that RyR2\^{R4496C} mice manifest a high incidence of sinoatrial node dysrhythmia (pauses) and an impaired positive chronotropic response to \(\beta\)-adrenergic stimulation. In RyR2\^{R4496C} sinoatrial node, there is an aberrant \(\text{Ca}^{2+}\) homeostasis characterized by an increase in the diastolic \(\text{Ca}^{2+}\) release at any time during the diastolic period. This almost continuous and low-grade \(\text{Ca}^{2+}\) leakage unloads the sarcoplasmic reticulum, which in turn hampers action potential triggering and decreases the sinus rate. We provide here a mechanistic rationale for sinoatrial node dysfunction in catecholaminergic polymorphic ventricular tachycardia patients. Future work should focus on testing pharmacological approaches to treat dysfunction of heart automaticity using this novel ex vivo physiological preparation. See p 392.

Childhood Physical, Environmental, and Genetic Predictors of Adult Hypertension: The Cardiovascular Risk in Young Finns Study

Hypertension is a major cardiovascular risk factor influenced by genetic propensity and various environmental stimuli. The present longitudinal study aimed to examine the best combination of childhood physical and environmental factors to predict adult hypertension. Furthermore, we examined whether newly identified genetic variants for blood pressure enhance the prediction of adult hypertension. In this longitudinal study, 2625 individuals who participated in the Cardiovascular Risk in Young Finns Study in the baseline year 1980 (when 3 to 18 years of age) were followed up 21 to 27 years (then 24 to 45 years of age). Youth risk factors independently associated with adult hypertension were the individual’s own systolic and diastolic blood pressures, parental hypertension, youth overweight/obesity, low parental occupational status, and high genetic risk score. We also found that both parental hypertension history and the genetic risk score enhanced the prediction of adult hypertension when added separately to the prediction model compared with the model consisting of only childhood blood pressure. Furthermore, the prediction power was significantly stronger when both of these variables were added to the same model. From these findings, it seems that the genetic risk score and parental hypertension provide complementary information. Present data suggest that a multifactorial approach, if implemented, could improve the identification of children with a high risk of adult hypertension. Moreover, these data demonstrate that the prediction of adult hypertension was enhanced when the novel genetic variants were taken into account. In terms of the care of individual patients with elevated blood pressure, our data emphasize the importance of overweight as a potential modifiable risk factor. See p 402.

Depressive Symptom Clusters and 5-Year Incidence of Coronary Artery Calcification: The Coronary Artery Risk Development in Young Adults Study

Evidence indicates that depression as a whole is an independent risk factor for coronary artery disease. Because depression consists of affective, cognitive, behavioral, and somatic symptoms, it is not clear whether certain symptom clusters are stronger risk factors for coronary artery disease than others. Accordingly, we compared the utility of depressive symptom clusters in predicting 5-year incidence of coronary calcification in 2171 healthy, middle-aged black and white community members. We found that the cluster of negative affective symptoms was the strongest predictor of incident coronary calcification. This relationship was independent of age, sex, race, education, and antidepressant use; was similar across sex and racial groups; and was partially explained by tobacco use and blood pressure. The results were driven primarily by responses to 3 depression questions (could not shake off the blues, felt depressed, and thought that life had been a failure) that are quick and easy to administer. Our findings suggest that, among middle-aged men and women, those experiencing the negative affective symptoms of depression are at increased risk of coronary calcification, in part because of their higher smoking rates and blood pressure levels. Concurrently addressing negative affective symptoms, smoking, and high blood pressure in these individuals may prevent the onset of coronary calcification, a strong predictor of future coronary artery disease events. See p 410.

Interleukin-10 Treatment Attenuates Pressure Overload–Induced Hypertrophic Remodeling and Improves Heart Function via Signal Transducers and Activators of Transcription 3–Dependent Inhibition of Nuclear Factor-κB

Chronic stress–induced hypertrophic growth of the myocardium leads to an increased risk of cardiovascular events, heart failure, and death. Experimental evidence suggests a potential role of inflammation in the progression of heart failure; however, the mechanisms of this process are not fully understood. The present study elucidates the novel therapeutic efficacy of the antiinflammatory cytokine interleukin-10 (IL-10) in both the prevention and attenuation of pathological hypertrophy and heart failure in 2 models of pressure overload. Additionally, our study provides the mechanism through which IL-10 imparts its therapeutic benefits for cardioprotection. The significance of the protective effect of IL-10 is further supported by an exaggerated adverse remodeling after pressure overload in IL-10 knockout mice. Importantly, we show that pretreatment of mice with exogenous recombinant IL-10 before either isoproterenol- or transverse aortic constriction–induced hypertrophic stimulus prevents ventricular remodeling, excessive fibrosis, and cardiomyocyte death and preserves left ventricular functions. Moreover, IL-10 treatment, once hypertrophy has been established, also attenuates adverse remodeling and fibrosis in animals with pressure overload. These findings that IL-10 therapy prevents cardiac remodeling and preserves cardiac function in the face of pressure overload stress have significant bearing not only on our understanding of the mechanisms involved in IL-10 action but also on the potential future clinical and therapeutic use of IL-10 and/or its downstream signaling components for the treatment of heart failure. Thus, IL-10 treatment may be a novel therapeutic approach to prevent and cure the hypertrophic cardiac remodeling in patients. See p 418.
Transplantation and Tracking of Human-Induced Pluripotent Stem Cells in a Pig Model of Myocardial Infarction: Assessment of Cell Survival, Engraftment, and Distribution by Hybrid Single Photon Emission Computed Tomography/Computed Tomography of Sodium Iodide Symporter Transgene Expression

Cardiac cell replacement therapies may significantly extend current therapeutic options for various cardiac diseases. The recently developed induced pluripotent stem cells are considered a major breakthrough with respect to the development of novel regenerative therapies and combine the advantages of adult and embryonic stem cells, namely, the availability of an autologous, ethically nonproblematic cell source with high potential for proliferation and differentiation into all cell lineages of interest. However, evaluation of novel cellular therapies in preclinical large-animal models and patients is currently hampered by the lack of suitable imaging approaches that allow long-term monitoring of viable transplanted cells. The present study was therefore designed to evaluate sodium iodide symporter transgene imaging as a novel approach to follow human induced pluripotent stem cell derivatives in a pig model of myocardial infarction. For the first time, our study demonstrates the usefulness of a sodium iodide symporter transgene for longitudinal in vivo tracking of survival, engraftment, and distribution of cellular grafts in a large-animal model with the use of single photon emission tomographic/computed tomographic imaging. Moreover, for the first time we demonstrate long-term survival and differentiation of human induced pluripotent stem cells in a preclinical pig model of myocardial infarction. The applied 3-dimensional hybrid imaging protocol enables combined assessment of cardiac anatomy and myocardial perfusion and monitoring of donor cell survival, proliferation, and distribution within 1 imaging modality. The developed approach will contribute to further optimization of novel cardiovascular cell–based treatment strategies and is of utmost importance for careful in vivo monitoring of associated risks such as potential tumor or teratoma formation. See p 430.

Statins and the Risk of Cancer After Heart Transplantation

Although newer immunosuppressive agents have lowered the incidence of malignancies after transplantation, cancer remains a leading cause of death late after heart transplantation. Because statins are immunomodulatory drugs and reduce the incidence of rejection and improve survival after cardiac transplantation, the present study investigated whether statin therapy impacts cancer risk as well as cancer-free and total mortality in heart transplant recipients. During follow-up, a malignancy was diagnosed in 108 patients (42%). Interestingly, the cumulative incidence of any malignancy was reduced in patients receiving a statin 8 years after transplantation (34% versus 13%, \( P=0.003 \)), and the benefit persisted at the 10-year and 12-year follow-up. In addition, statin use was associated with improved cancer-free and overall survival (both \( P<0.0001 \)). Statins reduced the hazard of occurrence of any malignancy by 67% (hazard ratio, 0.33; \( P<0.0001 \)). A Cox regression model that analyzed the time to tumor formation with or without statin therapy, adjusted for age, male sex, type of cardiomyopathy, and immunosuppressive therapy (including switching to mTOR [mammalian target of rapamycin] inhibitors or tacrolimus), demonstrated a decreased hazard for tumor formation in the statin group. Thus, in spite of limitations in adjusting for all potential confounders over a follow-up period of up to 25 years, during which factors related to the era of transplantation (such as overall intensity of immunosuppression and use of azathioprine) might have changed, the results of the present study suggest that statin use is associated with a substantial reduction of cancer risk and all-cause mortality in heart transplant recipients. Whether these benefits of statins are specific for heart transplant recipients who are at particularly high risk of cancer or can be extrapolated to all patients undergoing long-term immunosuppressive therapy (particularly with tacrolimus and mTOR inhibitors) needs to be confirmed in long-term randomized clinical trials. See p 440.

Development of a Clinical Prediction Rule for Risk Stratification of Recurrent Venous Thromboembolism in Patients With Cancer-Associated Venous Thromboembolism

Cancer patients who experience a venous thromboembolic event are at much higher risk of recurrent events while undergoing anticoagulation than any other patient group with similar events. As such, it can be argued that treatment is frequently ineffective, and new treatment strategies are warranted. However, given the heterogeneity of the cancer population, it is probable that not all cancer patients have this similar high risk. We have developed a prediction tool that enables us to identify a high-risk group with a risk of recurrence on the order of 20% and a low-risk group with a risk of recurrence on the order of 5%. This tool will allow us to identify patients in whom a closer vigilance is required and in whom new therapeutic strategies should be tested. The parameters used are very simple and include sex, primary tumor site and stage, and a history of prior venous thromboembolism. These are clinical parameters that are usually collected in all patients, thus ensuring the ease of use and applicability of this model. See p 448.

Histone Deacetylation Inhibition in Pulmonary Hypertension: Therapeutic Potential of Valproic Acid and Suberoylanilide Hydroxamic Acid

Histone deacetylases (HDACs) have emerged as key targets to reverse aberrant epigenetic changes associated with cancer and autoimmune disease, and HDAC inhibitors show promise as anticancer and antiinflammatory agents. We examined the pattern of HDAC expression in lungs from patients with pulmonary arterial hypertension and investigated the effect of HDAC inhibition on the reversal of pulmonary hypertension in a rat model. Coupled to this, we explored the effects on mechanisms (proliferation, apoptosis, and inflammation) relevant to the pathology of pulmonary arterial hypertension in human and animal cell model systems. Our results demonstrate that increased HDAC activity contributes to the vascular pathology of pulmonary hypertension. The effectiveness of the HDAC inhibitors valproic acid and suberoylanilide hydroxamic acid in models of pulmonary arterial hypertension supports a therapeutic strategy based on HDAC inhibition in pulmonary arterial hypertension. See p 455.

Nucleotide Excision DNA Repair Is Associated With Age-Related Vascular Dysfunction

Aging strongly contributes to cardiovascular disease. It prolongs exposure to classic cardiovascular risk factors such as hypertension and diabetes mellitus but also acts as an independent risk factor. Recent evidence suggests that gradually accumulating DNA damage, leading to genomic instability, is a main cause of aging. This study is the first to show that mice with a defective DNA repair system not only age fast but also display accelerated development of vascular problems mimicking those in aging humans: increased blood pressure, increased vascular stiffness, decreased vascular relaxation, and cellular aging. Of interest,
phosphodiesterase inhibition acutely improved the diminished relaxation in vitro, suggesting that enhanced breakdown of cGMP may underlie this phenomenon. Furthermore, in humans, variations in DNA repair genes were associated with markers for vascular aging. Taken together, these results indicate that genomic instability plays a central role in vascular aging. Genomic instability may also explain the high prevalence of cardiovascular death in Hutchinson-Gilford progeria and Werner progeroid syndrome, both of which feature genomic instability. Because oxidative stress is an important inductor of DNA damage, future aging-suppressor agents may involve drugs that improve genomic integrity (eg, statins and rapamycin) and drugs that prevent oxidative stress (eg, renin-angiotensin system blockers and antioxidants). In addition, drugs facilitating the nitric oxide–soluble guanylate cyclase–cGMP–phosphodiesterase pathway might be of value. The successful application of such treatments requires proper risk stratification, preferably at younger ages. This might include analyses of genetic variations in DNA repair genes and the identification of all possible sources of cardiovascular DNA damage. See p 468.