Upregulation of the Hyperpolarization-Activated Current Increases Pacemaker Activity of the Sinoatrial Node and Heart Rate During Pregnancy in Mice

An increased incidence of cardiac arrhythmias is observed during pregnancy. This may have significant consequences on the well-being of the mother and the fetus. In fact, during pregnancy the heart rate significantly increases, thus raising the susceptibility to arrhythmias. This is particularly true in the third semester, when sinus tachycardia becomes very common. Indeed, >50% of pregnant women exhibit a form of arrhythmia and ectopic beats. The mechanisms for the increase in heart rate and subsequent arrhythmia risks have been largely unexplored. In the present study we used a mouse model of pregnancy to explore the positive chronotropic effect in pregnancy, and we report one of the main underlying ionic mechanisms responsible for heart rate increase. First, we show that our mouse model of pregnancy reproduces the increased heart rate observed in pregnancy in humans and importantly that this increase is intrinsic to the heart and not secondary to alterations in autonomic tone, arterial blood pressure, or circulating catecholamine levels. We then demonstrate that pregnancy is associated with accelerated automaticity of the sinoatrial node cells through enhanced density of the funny current (If). 1 of the major ionic currents modulating pacemaker activity of the heart. Our results thus provide novel and functional insight into mechanisms of pregnancy-induced increase in heart rate. Additional work will be directed toward examining how these changes may initiate arrhythmias during pregnancy. As the number of pregnancies in women in an advanced maternal age—with more comorbidity—continues to rise, this issue is becoming even more relevant. See p 2009.

Safety of Sports for Athletes With Implantable Cardioverter-Defibrillators: Results of a Prospective, Multinational Registry

Although current recommendations restrict sports participation for patients with an implantable cardioverter-defibrillator (ICD), the risks are unknown. In this study, athletes with ICDs (age, 10–60 years) participating in organized (n=328) or high-risk (n=44) sports were followed up prospectively for median of 30 months, with sports-related and clinical data obtained by phone interview and medical records at baseline, if a shock occurred, and every 6 months. Median age was 33 years (89 subjects <20 years of age); 33% were female; and 42% had a pre-ICD history of ventricular arrhythmia. Sixty subjects were competitive athletes (varsity/junior varsity/traveling team). Running, basketball, and soccer were the most common sports. There were no occurrences of either primary end point—death or resuscitated arrest or arrhythmia- or shock-related injury—during sports. Shocks were not uncommon; there were 49 shocks in 37 participants (10% of study population) during competition/practice, 39 shocks in 29 participants (8%) during other physical activity, and 33 shocks in 24 participants (6%) at rest. In 8 ventricular arrhythmia episodes (device defined), multiple shocks were received: 1 at rest, 4 during competition/practice, and 3 during other physical activity. The ICD terminated all episodes. Freedom from lead malfunction was 97% at 5 years (from implantation) and 90% at 10 years, similar to that reported in unselected populations. In summary, many athletes with ICDs can engage in vigorous and competitive sports without physical injury or failure to terminate the arrhythmia, despite the occurrence of both inappropriate and appropriate shocks. These data provide a basis for more informed physician and patient decision making in terms of sports participation for athletes with ICDs. See p 2021.

Population-Based Study of Incidence and Outcome of Acute Aortic Dissection and Premorbid Risk Factor Control: 10-Year Results From the Oxford Vascular Study

This is the first prospective population-based study of acute aortic dissection with near-complete ascertainment of all aortic events over a 10-year period in a population of 92 478 in Oxfordshire, United Kingdom (2002–2010). We have shown that hospital-based registries will underestimate the incidence and case fatality of acute aortic dissection because of the exclusion of out-of-hospital deaths and that uncontrolled hypertension remains the most significant treatable risk factor. In addition, we have shown that the incidence of acute aortic dissection is higher than previously estimated and that, because of the ageing of populations and demographic changes, the numbers of cases are projected to almost double over the next few decades without more effective prevention. This has implications for health service provision and future research. See p 2031.

Monocyte-Directed RNAi Targeting CCR2 Improves Infarct Healing in Atherosclerosis-Prone Mice

The quality of infarct healing predicts the occurrence of heart failure. Primary cellular actors in wound healing in the heart are innate immune cells, including monocytes and macrophages; these cells orchestrate removal of dead tissue but also repair. Their inflammatory actions can hinder healing if they inhibit resolution of inflammation and rebuilding of extracellular matrix. The discovery of monocyte subsets and macrophage polarization has renewed interest in leukocyte-targeted therapies because subset-directed interventions promise to avoid collateral damage resulting from indiscriminate immunosuppression. A major hurdle for better understanding and therapeutically targeting innate immunity during healing of the heart is the lack of diagnostic tools. Our goal was to develop a method to follow infarct healing noninvasively. We quantified 2 targets that reflect antagonistic aspects of healing: Hybrid imaging of transglutaminase activity (positron emission tomography) and myeloperoxidase activity (magnetic resonance imaging) simultaneously reported on extracellular matrix organization and infarct inflammation. We tested the utility and predictive value of this positron
emission tomography/magnetic resonance imaging method to follow immunomodulatory therapy in a setting of impaired wound healing. Myeloperoxidase magnetic resonance imaging signal decreased when inflammatory monocytes were targeted with RNAi, whereas transglutaminase signal monitored extracellular matrix organization, potentially fatal collateral damage of immune modulation. Hybrid imaging strategies like the one described here may identify patients at risk for post–myocardial infarction heart failure and serve as a companion imaging strategy for future therapeutic interventions. See p 2038.

Mechanisms of Tissue Uptake and Retention in Zotarolimus-Coated Balloon Therapy

Local drug delivery from endovascular balloons investigated decades ago has been rejuvenated with the expectation that issues like thrombosis with drug-eluting stents and late lumen loss with bare metal stents could be avoided. Early failures of heparin-eluting catheters and balloons were attributed to poor retention of hydrophilic drugs, and, indeed, hydrophobic paclitaxel is retained, because it associates with hydrophilic carriers to enhance the transfer from blood to the artery wall and retains when dissociated. It remained unclear, however, whether sirolimus derivatives such as zotarolimus that are efficacious when released from drug-eluting stent but may not use the same transport-enhancing mechanisms as paclitaxel, could demonstrate comparable efficacy when coated on balloons. Our work is the first to describe the mechanisms of zotarolimus-coated balloon therapy by the use of an integrative approach coupling in vivo studies, bench-top experiments, and computational modeling. A large bolus of balloon-released zotarolimus and its constituents transfer during inflation, some drug pervades the tissue, and a fraction of the drug coating adheres to the tissue–lumen interface. The duration of balloon exposure to the tissue–lumen interface determines the net drug uptake into tissue, where diffusion mediates transport into the arterial wall and reversible binding to tissue ultrastructural elements determines the retention of zotarolimus in an arterial bed–dependent manner. Therefore, there is a theoretical basis for balloon delivery of zotarolimus to the arterial wall to be clinically efficacious and that optimization of zotarolimus-coated balloon therapy may rely on the tailoring of balloon coating, drug release kinetics, and inflation time to the arterial target. See p 2047.

Endocarditis in Adults With Bacterial Meningitis

Bacterial meningitis is a serious and life-threatening disease. The predominant causative pathogen is Streptococcus pneumoniae, causing two thirds of cases. Mortality rates associated with bacterial meningitis are high, and neurological and systemic complications occur in a large proportion of patients. One of the potential complications is endocarditis. Endocarditis may precede or complicate bacterial meningitis, but the incidence and impact of endocarditis in bacterial meningitis were unknown. In a large, prospective, nationwide cohort study of adults with community-acquired bacterial meningitis, we analyzed the incidence and clinical characteristics of patients with meningitis and endocarditis. We found that although endocarditis is an uncommon coexisting condition in bacterial meningitis, it is associated with a high rate of unfavorable outcome. The most common causative pathogens were S pneumoniae and Staphylococcus aureus. Clues leading to the diagnosis of endocarditis were cardiac murmurs, persistent or recurrent fever, preexisting heart valve disease, secondary clinical deterioration, S aureus as the causative pathogen, atrial flutter, and splinter hemorrhages. This study indicates that cardiology consultation should be a priority in patients with community-acquired meningitis presenting with clues for endocarditis. Because about half of patients with pneumococcal meningitis have either persistent or recurrent fever, many future patients with pneumococcal meningitis will need ancillary investigations to rule out or to establish endocarditis. In most patients, endocarditis was diagnosed during hospitalization or even after discharge, so early detection of endocarditis in patients with bacterial meningitis may lower the rate of complications and unfavorable outcome. See p 2056.