ANIMAL MODELS IN CARDIOVASCULAR RESEARCH

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Cardiovascular diseases (CVDs) are a major cause of morbidity and mortality worldwide. Although many therapeutic means are available to prolong the life of CVD patients, the mechanisms underlying the development and progression of heart failure and its propensity to arrhythmias are still poorly understood. Investigators still seek truly appropriate animal models that will reliably mimic human CVDs, so that the cause of the disease can be targeted and proper therapeutic modalities implemented. Such an approach is complicated by the fact that CVDs are complex and multifactorial conditions in which multiple molecular mechanisms interact, resulting in compromised cardiac function and sudden death. In the last years, we have been using rat models of cardiac hypertrophy and failure as well as models of diabetic cardiomyopathy that allowed us to study the electrophysiological remodeling which accompanies the development and progression of heart disease toward heart failure. Remodeling is known to occur in all forms of heart disease, developing as a consequence of myocardial infarction, pressure overload, idiopathic dilated cardiomyopathy, diabetes etc., and involves the myocyte, the interstitium and the vasculature. This process, initially adaptive, often becomes maladaptive, leading to progressive decompensation and predisposing to arrhythmias and sudden death. The risk of sudden death progresses with heart disease and likely reflects changes in electrophysiological substrate. Animal models of cardiac hypertrophy may be helpful for understanding events occurring in the diseased human heart. In particular, two arrhythmogenic mechanisms have been consistently reported: a prolongation of action potential, due to a reduction of repolarizing potassium currents and the expression of the hyperpolarization-activated current, I_f. Interestingly, similar abnormalities have been observed in human cardiomyocytes from human failing hearts. Pharmacological interventions such as in-vivo treatment with angiotensin-II receptor blockers, are able to restore cellular functional properties. In conclusion, appropriate models for the study of heart diseases may lead to a deeper understanding of arrhythmogenic mechanisms - in terms of cellular and tissue electrophysiology of the failing heart - and promote the development of novel therapeutic strategies in this setting.