Sudden cardiac death (SCD) is the most common cause of cardiovascular-related death, accounting for more than 50% of all cardiovascular mortality worldwide. SCD is often the first manifestation of unrecognized cardiac disease. Ventricular tachyarrhythmias, mainly ventricular fibrillation, are primarily responsible for the mechanism underlying most SCD episodes. Ventricular tachyarrhythmias occur frequently in the setting of coronary artery disease with or without the presence of myocardial infarction. In spite of the prevalence of defibrillation programs, and frequent attempts made to resuscitate patients experiencing SCD, the survival rate after SCD was substantially unsatisfactory. Most SCD episodes occur in individuals without previously known cardiac disease, further making the inability to successfully identify and properly treat this disease a critical public health problem.

Ventricular fibrillation accounts for most of the deaths occurring in the acute phase of ischemia (within hours to days), whereas sustained, monomorphic ventricular tachycardia due to reentry generated in the scar tissue usually develops in the setting of a healed myocardial infarction (typically weeks to months). There is a distinction in arrhythmias occurring in the subacute phase of myocardial infarction and in the chronic phase. The electrophysiological mechanisms involved with arrhythmia generation and electrical remodeling have been extensively studied. In addition, SCD as the result of ventricular tachyarrhythmias is the most ominous presentation of myocardial infarction. SCD in the immediate period after myocardial infarction represents a clinical challenge, particularly in patients with left ventricular dysfunction or heart failure. It is now well established that ventricular tachyarrhythmia in the setting of infarction is a reentrant arrhythmia where cells in the infarct border have normal action potentials but display slow and discontinuous conduction, which is associated with abnormal connexin expression. Furthermore, it has been noticed that only a minority of patients who have been successfully resuscitated from SCD associated with coronary artery disease subsequently developed a myocardial infarction. The pathophysiology and electrophysiology involved with reperfusion arrhythmia and SCD are distinct from those in the setting of ischemia and infarction.

Beyond ischemia-reperfusion etiology, ventricular tachyarrhythmia and SCD are attributed to genetic arrhythmia syndromes and cardiomyopathies. Because such events are almost always catastrophic or fatal at presentation, it is impossible to conduct complete human studies in elucidating and exploring the mechanisms, including abnormal excitability, conduction, or repolarization, and underlying molecular or cellular biology leading to SCD. Our current knowledge of arrhythmias stems from animal models serving as surrogates for humans. Beyond mechanism studies, a stable and reproducible animal model is helpful to evaluate novel antiarrhythmic compounds and to study proarrhythmic effects of both cardiac and noncardiac therapeutic agents.

In this issue of the Journal, Dr. Chen and his colleagues established a swine model of ischemic SCD. The middle portion of the left anterior descending coronary artery was blocked by the balloon catheter to control the infarction area. Myocardial infarction was confirmed by electrocardiograms and pathological examinations, and ventricular tachyarrhythmia and SCD were confirmed by continuous electrocardiographic recordings. They successfully induced ventricular fibrillation and SCD in 16 of 20 of their animals and were unable to secure seven animals from recurrent ventricular fibrillation. This closed-chest technique is less traumatic and more similar to pathophysiology that occurs in humans during ischemic insults compared with the open-chest ligation method. In addition, the coronary characteristics and cardiac electrophysiological properties in swine are similar in those of humans.

Several points should be acknowledged. First, this swine model is at best a simulation of the clinical phenotype. The techniques used to establish myocardial infarction in this model were different from the pathophysiology responsible for myocardial infarction in most patients in the clinical setting. Some information obtained from studies on nonprimate mammals may not be extrapolated to humans. Second, the study was conducted on anesthetized animals, which might have differences in thresholds for ventricular arrhythmias. The use of anesthetics in studying ventricular arrhythmias is contentious, because some directly alter arrhythmogenicity and others alter autonomic efferent traffic, which affects arrhythmogenicity. Third, in the current model there was no electrophysiology study to induce ventricular tachyarrhythmias in the surviving animals. Fourth, the current model constructed in the setting of ischemic myocardium is not applicable to non-ischemic SCD, particularly cardiomyopathy and genetic arrhythmia-related SCD.
Death from ventricular arrhythmia remains an important challenge in medicine. The animal models are necessary because they allow for controlled studies and methods of exploration that, for legal and ethical reasons, are not possible in humans. A successful animal model mimicking human structural and electrophysiological properties is important in understanding the genesis of such a fatal condition, and is essential in the development of therapeutic strategies.

References


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