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REVIEW

Experimental Models of Spontaneous Ventricular Arrhythmias and of Sudden Cardiac Death

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Summary

Sudden cardiac death defined as natural death from cardiac causes occurring within one hour of the onset of acute symptoms is one of the most significant non-injury causes of death in the adult population of industrialised countries. The understanding of the mechanisms leading to sudden cardiac death is so far limited. Recently, a number of experimental animal models with high incidence of sudden cardiac death were developed and are intensively studied to get new insights into the sudden cardiac death mechanisms. In this review the animal models of sudden cardiac death are summarized and their principal properties shortly described.

Key words

Heart • Sudden cardiac death • Experimental animal model

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Sudden cardiac death

Cardiovascular disease is the most frequent cause of death in the world; in the Czech Republic it accounts for 52 % of all deaths (Institute of Health Information and Statistics of the Czech Republic). One of the most significant non-injury causes of death in the adult population of industrialised countries is sudden cardiac death, defined as natural death from cardiac causes occurring within one hour of the onset of acute symptoms. Sudden cardiac death represents ~10 % of all natural deaths (Kuller *et al.* 1967) and approximately 2/3 of all sudden non-trauma deaths in the adult population (Thomas *et al.* 1988). For about 3/4 of those afflicted by sudden cardiac death, coronary artery disease is present and sudden cardiac death can be the first manifestation of this disease. The prevalence of sudden cardiac death is also higher in cardiomyopathy (hypertrophic, dilated, right ventricle). The risk factors for sudden cardiac death therefore correspond to the risk factors for coronary atherosclerosis and include, e.g., increased LDL cholesterol, obesity, hypertension, diabetes and smoking (Priori *et al.* 2001). Nevertheless, in about five to ten percent of cases, sudden cardiac death occurs with no presence of coronary disease or cardiomyopathy. It is likely that these cases predominantly represent arrhythmogenic syndromes (channelopathies) which increase the risk of ventricular tachyarrhythmia and sudden cardiac death without significant structural changes of the heart (long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia) (Priori *et al.* 2002a, 2002b, 2003). The predominant mechanism of sudden cardiac death is ventricular tachyarrhythmia, particularly ventricular fibrillation (Zipes *et al.* 2006). The processes that lead to the onset (and maintaining) of ventricular fibrillation, however, remain unexplained. Given the variable initial heart conditions (from a structurally normal heart to cardiac hypertrophy, acute ischemia or cardiac arrest), the processes are likely multifactorial and dynamic. At a given moment in a given person, the combination of one or more trigger events

(acute ischemia, physical activity, mental stress, ionic changes) with the appropriate myocardial substrate (hypertrophic myocardium, ischemic myocardium, failing myocardium, myocardium with channelopathy) will subsequently lead to the onset of fatal ventricular tachyarrhythmia and sudden cardiac death. Besides changes on the level of cardiac myocytes (electric, contractile and structural remodelling), changes in the cardiac autonomous innervation (neural remodelling) also play a role (Efimov 2003). Detailed understanding of the mechanisms leading to sudden cardiac death is absolutely necessary for developing methods that will allow determining with sufficient reliability which individuals are at significantly high risk of sudden cardiac death. Given the prevalence of sudden cardiac death, which is about 1/1000/year among the European and North American population (Priori *et al.* 2001, Zipes *et al.* 2006), whole-population interventions are impossible and the only meaningful strategy appears to be identifying individuals with an increased risk of sudden death and applying individualised preventative measures for these patients. For investigation of mechanisms leading to sudden cardiac death and determination of risk indicators the experimental animal models with high incidence of spontaneous ventricular arrhythmias and of sudden cardiac death are absolutely necessary.

Mouse/rat models

With the development of transgenic animal technology a huge (and still growing) number of various experimental mouse/rat models appeared. From point of view of cardiac electrophysiology and arrhythmology, however, a substantial limitation of these models must be taken into account: Mouse cardiac electrophysiological characteristics are significantly different from those of human. The duration of mouse cardiac action potential is very short; the plateau phase is not present. The major ionic currents contributing to action potential are different from those in human (for review see Nerbonne 2004). Heart rate of mice is extremely high (resting heart rate of 600 bpm). Due to these differences, the translation of the results obtained in mouse studies to human physiology and clinic must be very cautious.

Transgenic mouse with long-QT3 syndrome

The mouse with long-QT3 syndrome (LQT3) was one of the first mouse models of proarrhythmia (Nuyens *et al.* 2001). Consistent with LQT3 patients, a deletion of amino-acid residues 1505-1507 (KPQ) in the cardiac sodium channel, encoded by SCN5A gene, caused an abnormal prolongation of repolarization associated with fatal ventricular arrhythmias. The inactivation of sodium channel was impaired producing an additional depolarizing current I_{NaL} (late sodium current). As an unexpected feature, a paradoxical lengthening of repolarization with early afterdepolarization and triggered arrhythmias in response to sudden heart rate acceleration or premature beats was found. The relevance of this novel arrhythmogenic mechanism for LQT3 patients remains to be determined.

Transgenic mouse with cardiac-restricted knockout of connexin43

Mice with cardiac-specific loss of connexin43 have normal heart structure (normal left ventricular chamber size and wall thickness) and contractile performance (assessed by echocardiography in 1-month-old mice), however they develop uniformly sudden cardiac death from spontaneous ventricular arrhythmias within 2 months of age (Gutstein *et al.* 2001). Ventricular conduction velocity was significantly slowed in both transverse (by up to 55 %) and longitudinal (by 42 %) directions. The findings clearly document the essential role of gap junctions/connexin43 in the maintenance of electrical stability of the heart.

Transgenic mice with suppression of cardiac potassium currents

To investigate the contribution of potassium currents to cardiac repolarization and dispersion of repolarization and the role of dispersion of repolarization in promoting arrhythmia, London *et al.* (2007) engineered mouse models which lack $I_{to,f}$ (rapidly activating, rapidly inactivating transient outward potassium current encoded by Kv4.2), $I_{to,s}$ (a more slowly inactivating component of the transient outward current encoded by Kv1.4) or both. Mice that lacked $I_{to,f}$, had action potential and QT-interval prolongation, but no spontaneous arrhythmia. Mice that lacked $I_{to,s}$, had no QT-interval prolongation and no arrhythmia. Mice that lacked both $I_{to,f}$ and $I_{to,s}$, had action potential and QT-interval prolongation, and spontaneous ventricular arrhythmias. Dispersion of repolarization was only increased in mice that lacked both $I_{to,f}$ and $I_{to,s}$. Thus, elimination of repolarizing potassium currents may lead to increased dispersion of repolarization and the dispersion of repolarization appears to be an important determinant of arrhythmia vulnerability.

Mouse/rat models of cardiomyopathies

A huge number of mouse/rat models were developed for investigation of pathways involved in pathogenesis of cardiomyopathy. A variety of gene mutations may finally manifest as cardiomyopathy. Hypertrophic cardiomyopathy is typically caused by mutations in genes encoding proteins of the sarcomere. Dilated cardiomyopathy may be related to mutations in genes for proteins of sarcomere, cytoskeleton and nuclear envelope. Arrhythmogenic right ventricular cardiomyopathy is caused mainly by mutations in genes encoding proteins of desmosomes, which are the intercellular junctions linking the cardiomyocytes. From various models of cardiomyopathies available nowadays a number of them are associated with increased susceptibility to arrhythmias and sudden cardiac death. A comprehensive review of current animal models for inherited arrhythmogenic cardiomyopathies was published recently (McCauley and Wehrens 2009).

Rabbit models

The rabbit ventricular action potentials resemble the human ventricular action potentials much more than those of mouse or rat. The action potential shows the typical positive plateau phase and the duration approaches the values in human. All major ionic currents contributing to human ventricular action potential are present in rabbit ventricular cells, although some quantitative and kinetic differences may be identified. The small size of the rabbit heart (compared to human) may limit some spatial phenomena like transmural heterogeneity of action potentials. Anyway, compared to mouse, the results obtained in rabbit cardiac preparations should be more relevant and easier to translate to the human physiology.

Transgenic rabbit with long-QT syndrome

Expression of pore mutants of the human genes KCNQ1 and KCNH2 in the rabbit heart produced phenotypes of long-QT1 and long-QT2 syndromes, respectively (Brunner *et al.* 2008). Analysis of the transgenic rabbits revealed that the prolongation of QT-interval and action potential duration was due to elimination of I_{Ks} and I_{Kr} currents, respectively. Long-QT2 rabbits showed a high incidence of spontaneous sudden cardiac death (>50 % at 1 year) due to polymorphic ventricular tachycardia. Optical mapping studies revealed increased spatial dispersion of repolarization underlying the re-entrant arrhythmias in long-QT2 rabbits. Interestingly, the elimination of 1 repolarizing current (e.g. I_{Kr}) was associated with downregulation of the other current (e.g. I_{Ks}), in contrast to compensatory upregulation found in mouse long-QT models (Guo *et al.* 1999, 2000).

Rabbit with chronic atrioventricular block

Chronic complete atrioventricular block in the rabbit led within several weeks to biventricular hypertrophy, prolongation of QT-interval and action potential duration and spontaneous torsade de pointes arrhythmias (Tsuji *et al.* 2002). The prolongation of repolarization was due to downregulation of potassium repolarizing currents I_{Ks} and I_{Kr}. All noneuthanized rabbits died suddenly between 0 and 38 days of escape rhythm. The linear relationship between the date of first torsade de pointes arrhythmia event and survival period suggests the arrhythmic mechanism of death, however, at least in some rabbits the heart failure cannot be excluded.

Hypercholesterolemic rabbit

Hypercholesterolemic diet fed for 12 weeks induced a pronounced hypercholesterolemia that was associated with electrophysiological and neural remodeling of the heart (Liu *et al.* 2003). Only minimal coronary atherosclerosis was observed in epicardial coronary arteries and there was no evidence of myocardial infarction. The electrophysiological remodeling was characterized by prolongation of QT interval and action potential duration, increased QT dispersion and heterogeneity of repolarization and higher calcium current density. The neural remodeling involved significant nerve sprouting and sympathetic hyperinnervation. Cardiac hypertrophy was also present in hypercholesterolemic rabbits. Together the electrophysiological and neural remodelings resulted in increased vulnerability to ventricular fibrillation.

Dog models

From the point of view of cardiac electrophysiology, the canine heart appears to be the most relevant model for studying and translating mechanisms of arrhythmias. The major ionic currents correspond well to those in human myocardium. Duration and shape of action potential and heart rate approach the human values. The size of the heart is sufficient to study conveniently the spatial phenomena involved in

arrhythmogenesis like heterogeneity of repolarization or spread of excitation.

Dog with chronic atrioventricular block

The bradycardia-induced volume overload due to the chronic atrioventricular block results within several weeks in complex structural, contractile and electrophysiological remodelling. Cardiac hypertrophy was observed on both organ and cellular levels (Volders *et al.* 1998, Vos *et al.* 1998). Contractile remodelling compensates the cardiac output and it is associated with enhanced calcium release (de Groot *et al.* 2000, Sipido *et al.* 2000). Electrophysiological remodelling comprises downregulation of potassium currents I_{Ks} and I_{Kr} (Volders *et al.* 1999) and upregulation of sodium-calcium exchanger (Sipido *et al.* 2000). All these alterations predispose to torsade de pointes arrhythmia and sudden cardiac death (Vos *et al.* 1995, van Opstal *et al.* 2001).

German shepherd dogs with inherited ventricular arrhythmia and sudden cardiac death

A colony of German shepherd dogs that exhibit inherited ventricular arrhythmia and sudden arrhythmic death was established (Moise *et al.* 1997). The incidence of arrhythmias increased with age (between 7 and 28 weeks of age) and was related to age-dependent reduction in sinus rate. Abnormal heterogeneous cardiac sympathetic innervation, decreased density of potassium current I_{to}, abnormal calcium handling and spatial heterogeneity in ventricular I_{Kr} expression probably contribute to the arrhythmic phenotype of these dogs (Dae *et al.* 1997, Freeman *et al.* 1997, Steinberg *et al.* 2002, Obreztchikova *et al.* 2003).

Boxer dogs with arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy is an inherited cardiac disease associated with substantial cardiovascular morbidity and sudden death in young people (Thiene *et al.* 1988). Causative mutations were identified in genes encoding desmosomal proteins (Basso *et al.* 2009). A spontaneous, genetically transmitted model of arrhythmogenic right ventricular cardiomyopathy, closely resembling the human disease, was described in boxer dogs (Basso *et al.* 2004). Clinical events included sudden death, ventricular arrhythmias of suspected right ventricular origin, syncope and heart failure. Severe right ventricular myocyte loss with replacement by fatty or fibrofatty tissue was present. The cardiomyopathy in the model was shown to be associated with a substantial loss of gap junction plaques as well as with remodeling of other intercalated disc structures (Oxford *et al.* 2007). Calstabin2 deficiency associated with a significantly increased open probability of single sarcoplasmic reticulum release channels was also identified and suggested as a potential mechanism for calcium leak-induced ventricular arrhythmias in these dogs (Oyama *et al.* 2008).

Pig models

Similar to dog, the pig heart also represent a good model highly relevant for human cardiac electrophysiology, in many aspects similar to human heart. A significant electrophysiological difference is the lack of potassium current I_{to} (Li *et al.* 2003, Schultz *et al.* 2007) that is present in human as well as in canine myocardium.

Pig with hibernating myocardium

Pigs with hibernating myocardium arising from a chronic coronary artery occlusion have a high rate of sudden cardiac death, cumulative mortality attributable to sudden cardiac death being 49 % after 5 months (Canty *et al.* 2004). Ventricular fibrillation was documented as the arrhythmic mechanism of death. Action potential prolongation in hibernating myocytes was documented (Bito *et al.* 2004) and the increased electrical heterogeneity of the myocardium could contribute to the arrhythmogenic substrate. Spatial inhomogeneity of sympathetic innervation in hibernating myocardium may be another factor contributing to lethal arrhythmias (Luisi *et al.* 2002).

Conclusions

A significant number of animal models with high incidences of lethal ventricular arrhythmias are available nowadays for studying the mechanisms of sudden cardiac death. The wide range of models documents the variety of sudden cardiac death mechanisms when a particular combination of a trigger event with a myocardial substrate in a given individual results in sudden death. A detailed understanding of the mechanisms leading to sudden cardiac death is absolutely necessary for development of diagnostic, preventive and therapeutic strategies that will in the end reduce the risk of sudden cardiac death in the population. Obviously the

translation of experimental results obtained in animal models to patient will be an ambitious and difficult task. Interpretation of various sudden death mechanisms occurring in the models will be always complicated by species differences. In this respect the comparative (patho)physiology must be taken into account and complement the translational efforts.

Conflict of Interest

There is no conflict of interest.

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