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COMPENDIUM ON BASIC MODELS OF CARDIOVASCULAR DISEASE

Animal Models to Study Cardiac Arrhythmias

Daniel J. Blackwell, Jeffrey Schmeckpeper, Bjorn C. Knollmann

ABSTRACT: Cardiac arrhythmias are a significant cause of morbidity and mortality worldwide, accounting for 10% to 15% of all deaths. Although most arrhythmias are due to acquired heart disease, inherited channelopathies and cardiomyopathies disproportionately affect children and young adults. Arrhythmogenesis is complex, involving anatomic structure, ion channels and regulatory proteins, and the interplay between cells in the conduction system, cardiomyocytes, fibroblasts, and the immune system. Animal models of arrhythmia are powerful tools for studying not only molecular and cellular mechanism of arrhythmogenesis but also more complex mechanisms at the whole heart level, and for testing therapeutic interventions. This review summarizes basic and clinical arrhythmia mechanisms followed by an in-depth review of published animal models of genetic and acquired arrhythmia disorders.

Key Words: atrial fibrillation ■ cardiomyopathies ■ channelopathies ■ models, animals ■ morbidity

Cardiac arrhythmias affect ≈2% of community-dwelling adults, with an incidence of ≈0.5% per year.[1] Arrhythmias can manifest as relatively benign entities, such as atrial and ventricular premature beats, or as life-threatening arrhythmias such as ventricular tachycardia (VT) and ventricular fibrillation (VF), which can lead to sudden cardiac death (SCD), accounting for 10-15% of all deaths in the United States. Atrial fibrillation (AF) accounts for the greatest arrhythmia burden and is associated with stroke and heart failure, fueling huge health care costs. Arrhythmia treatment approaches focused on risk factor reduction, drug therapy, catheter ablation, device implantation, or a combination of these strategies has improved morbidity and mortality over the last 20 years, but treatment with antiarrhythmic drugs is often ineffective or increases mortality long term.[2,3] A more thorough understanding of the pathophysiology of arrhythmia initiation and maintenance is important for improving clinical outcomes.

The mechanisms underlying arrhythmogenesis at the cellular level involve ion channels and electrogenic transporters that are altered via biogenic (synthesis, processing, trafficking, and degradation), biochemical (post-translation modification, phosphorylation), and biophysical (gating, permeation) processes (reviewed here in study by Delisle et al[4]). The interplay between ion channels and transporters controls the action potential duration (APD), effective refractory period, and Ca^{2+} cycling to coordinate excitation-contraction coupling and normal myocyte function; dysregulation leads to abnormal cardiomyocyte electrical activity.[5] Structural and hemodynamic parameters contribute to further cardiac remodeling, increasing the risk for arrhythmia development and maintenance.[6–9]

To study underlying arrhythmia mechanisms and evaluate treatment approaches, multiple in vitro systems and in vivo models have been developed. This review focuses on animal models that have informed our understanding of arrhythmia pathophysiology and have been used to develop new therapeutic approaches. An ideal model would recapitulate human anatomic, electrophysiological, and hemodynamic parameters. Currently, no single model can accomplish this feat. However, animal models have enabled the discovery of new treatment strategies for humans with genetic arrhythmia disorders. For example, mouse models demonstrated the efficacy of flecainide in catecholaminergic polymorphic ventricular tachycardia[10] and mexiletine in long QT type 3.[11] When choosing an animal model of cardiac arrhythmia, researchers must consider the most appropriate model to address a specific scientific question based on cost, complexity, ease of handling, access to diagnostic and surgical expertise, and the ability for genetic modification.

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Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
AP	action potential
APD	action potential duration
ARVC	arrhythmogenic right ventricular cardiomyopathy
AT	atrial tachycardia
BrS	Brugada syndrome
CHB	complete heart block
CPVT	catecholaminergic polymorphic ventricular tachycardia
CRDS	Ca^{2+} release deficiency syndrome
DAD	delayed afterdepolarization
DCM	dilated cardiomyopathy
DSC2	desmocollin-2
DSG2	desmoglein-2
EAD	early afterdepolarization
ECM	extracellular matrix
HCM	hypertrophic cardiomyopathy
LQTS	long QT syndrome
MAT	multifocal atrial tachycardia
MPO	myeloperoxidase
PES	programmed electrical stimulation
PKP2	plakophilin-2
PLB	phospholamban
PVC	premature ventricular contraction
SCD	sudden cardiac death
SQTS	short QT syndrome
SR	sarcoplasmic reticulum
SVT	supraventricular tachycardia
TAC	transverse aortic constriction
TdP	Torsades de Pointes
TGF	transforming growth factor
VF	ventricular fibrillation
VT	ventricular tachycardia

Here, we provide the reader with a brief overview of basic and clinical cardiac electrophysiology, followed by an in-depth review of existing animal models of cardiac arrhythmias. Animal models are classified as either genetic (ie, arrhythmia risk caused by gene mutation) or acquired (ie, arrhythmia risk caused by nongenetic heart diseases such as myocardial infarction, metabolic abnormalities, or cardiac hypertrophy).

PRINCIPLES OF CARDIAC ELECTROPHYSIOLOGY

The Cardiac Conduction System

Normal heart rhythm is generated and regulated in the specialized cardiac conduction system, which consists of the sinoatrial node, the atrioventricular (AV) node, and the HIS-Purkinje system (Figure 1). Electrical impulses are initiated in the sinoatrial node and spread through the atria to the AV node. After a slight delay (0.12–0.20 seconds), excitation continues through the bundle of His, the right and left bundle branches, and finally the Purkinje fibers, which then excite the working myocardium. The delay in the AV node allows the atria to contract earlier than the ventricles and provides adequate time for optimal ventricular filling.[12] The specialized cells within the sinoatrial node, AV node, and His-Purkinje system are capable of spontaneous depolarization that is regulated by both the sympathetic and parasympathetic nervous system. Conduction through the heart depends on electrical coupling between cells, which is mediated by gap junctions.

Species Differences in the Cardiac Action Potential and Cardiac Ca^{2+} Handling

The cardiac action potential (AP) results from the opening and closing of ion channels and electrogenic transporters in the plasma membrane of individual cardiomyocytes (see study by Varró et al[13] for details). Figure 2 illustrates AP wave forms and underlying membrane currents for ventricular cardiomyocytes of humans and mice.

When choosing an animal model for arrhythmia research, it is important to recognize species differences in cardiac AP and membrane currents, which are the result of species-specific expression of ion channels and transporters. For example, unlike humans, mice and rats have a low AP plateau at ≈—40 mV membrane potential (Figure 2). This is primarily the result of differential expression in repolarizing transient K-currents, as illustrated in Figure 2. On the other hand, rabbits and guinea pigs have a more positive AP plateau analogous to humans.[14] For a more detailed comparison of ionic currents in different species, the reader is referred to here.[15]

As with the AP, there are important species differences in cardiac Ca^{2+} handling. For example, mice and rats primarily (>90%) utilize sarcoplasmic reticulum (SR)-mediated Ca^{2+} cycling (via the cardiac ryanodine receptor [RyR2] and the SR Ca uptake pump [SERCA2a]) for excitation-contraction coupling, whereas in humans, dogs, and rabbits the SR accounts for ≈65%, with the remainder coming from outside the cell via the L-type Ca channel ($Ca_V1.2$) and the NCX (Na/Ca exchanger).[16] For a more detailed comparison of species differences in Ca^{2+} handling, the reader is referred to here.[17]

Pathophysiology of Cardiac Arrhythmias

The main mechanisms of arrhythmogenesis can be divided into either abnormal impulse generation or abnormal impulse propagation. Disorders of impulse generation and propagation, regulation of the AP duration, and cellular

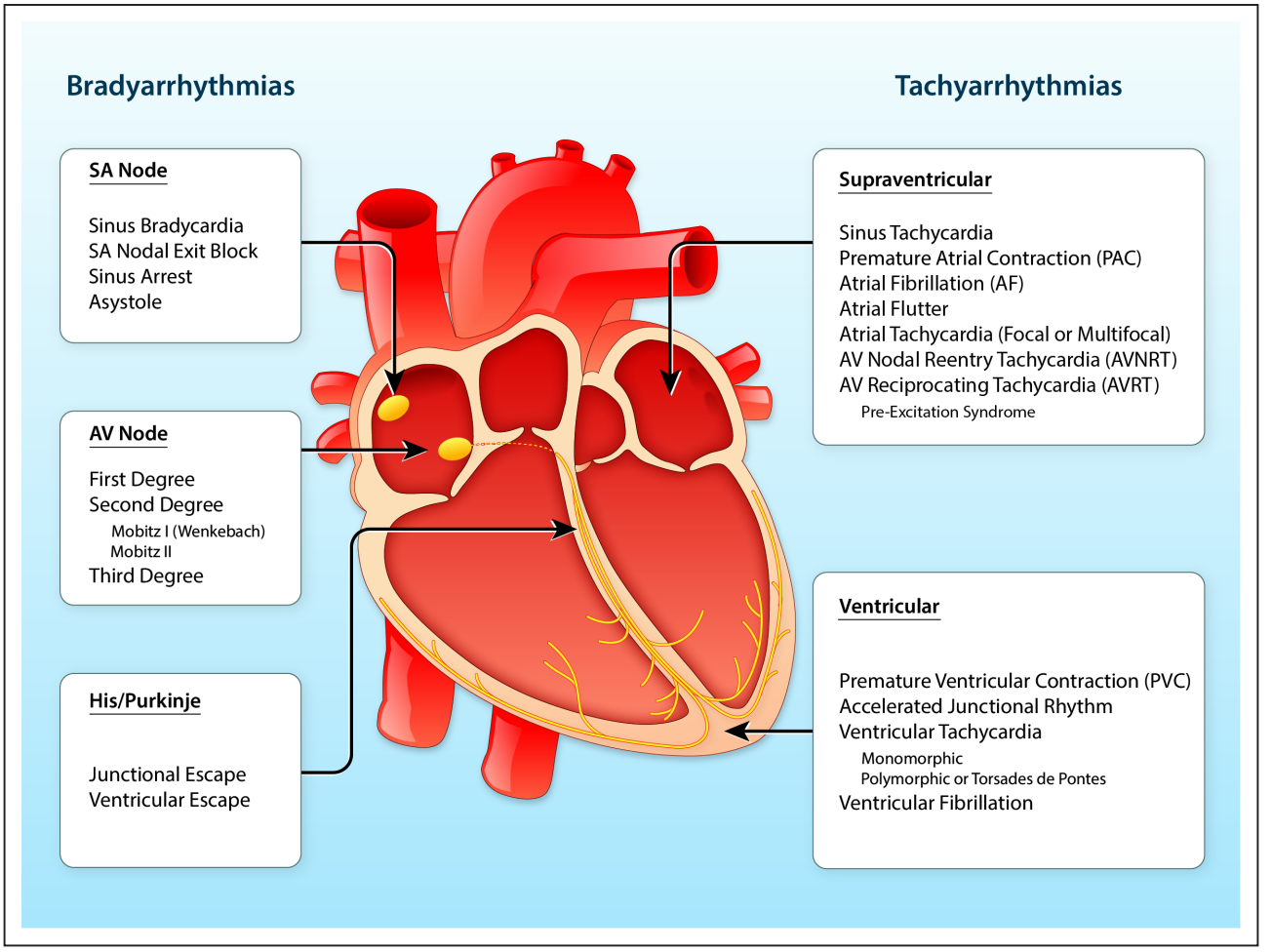

Figure 1. Schematic of the cardiac conduction system and clinical classification of cardiac arrhythmias.
AF indicates atrial fibrillation; AV, atrioventricular; AVNRT, AV nodal reentry tachycardia; AVRT, AV reciprocating tachycardia; PAC, premature atrial; and SA, sinoatrial. Illustration credit: Ben Smith.

substrates can all contribute to 3 categories of arrhythmias; enhanced automaticity, triggered ectopic beats, and reentry. Each arrhythmia category is explained briefly below. A more detailed review can be found in here.[5]

Automaticity

Automaticity is the ability of cells to generate their own AP.[18] The intrinsic depolarization rate of the sinoatrial node is faster than the rest of the cardiac conduction system and overdrives pacemaking in the AV node and His-Purkinje system. However, automaticity in the AV node and His-Purkinje system can become dominant in sinoatrial nodal dysfunction. The sinoatrial node is more sensitive to increased sympathetic and parasympathetic tone, leading to sinus tachycardia and bradycardia, respectively. Under normal conditions, atrial and ventricular cardiomyocytes display either no or very slow intrinsic depolarization that are easily suppressed by the faster, coordinated impulses from the sinoatrial node through the conduction system. Increased automaticity in the atria can lead to focal and multifocal atrial tachycardia and AF. Specifically, the pulmonary vein sleeve, where the left atria myocytes transition to the tunica media of the pulmonary veins, is known to harbor tissue with increased automaticity,[19] and is a target for catheter based ablation by pulmonary vein isolation for AT and AF. Increased automaticity in the ventricle is less common but can lead to VT or accelerated idioventricular rhythms.

Afterdepolarizations and Triggered Arrhythmia

Triggered arrhythmias are because of spontaneous membrane depolarization of atrial or ventricular myocytes that precede the next sinus beat. Membrane depolarizations that occur within or follow the cardiac AP are referred to as afterdepolarizations. Two classes are traditionally recognized: early and delayed. An early afterdepolarization (EAD) interrupts the repolarization during phase 2 or early phase 3 of the cardiac AP, whereas a delayed afterdepolarization (DAD) occurs after full repolarization in Phase 4. When an EAD or DAD brings the membrane to its threshold potential, a spontaneous AP is referred to as a triggered response. These triggered events can give rise to premature extrasystolic complexes in the atria or the ventricle (PVCs), precipitating tachyarrhythmias. In general, any unbalanced increased inward current (ie, gain-of-function

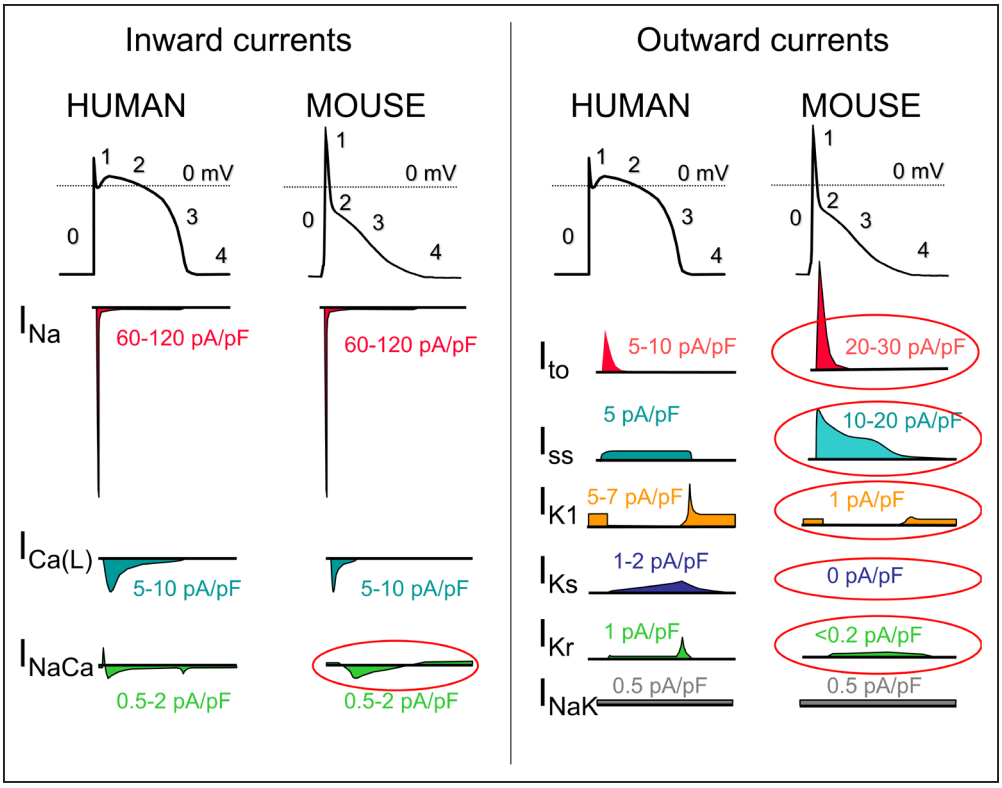

Figure 2. The ventricular action potential and ionic currents in humans and mice.
Note the differences in action potential shape, which is caused primarily by differences in ionic currents circled in red. $I_{Ca(L)}$ indicates L-type Ca current; $I_{Ca(T)}$, T-type Ca current; I_{Na}, Na current; I_{NaCa}, Na-Ca-Exchange current; I_{NaK}, NaK-ATPase pump current; I_{K1}, Inward rectifier K-current; I_{Kr}, rapidly activating delayed rectifier K-current; I_{Ks}, slowly activating delayed rectifier K-current; I_{ss}, rapidly activating steady-state K-currents; and I_{to}, transient outward K-current. Please note that current densities (pA/pF) measured in single cells vary drastically with experimental conditions and voltage clamp protocols. Current densities were chosen to reflect relative contributions to the AP.

mutations in Na^+ or Ca^{2+} channels) or decreased outward currents (ie, loss-of-function mutations in K^+ channels) will depolarize the cell membrane and can lead to EADs or DADs.[20] Specifically, a major cause of triggered arrhythmia is spontaneous RyR2-mediated SR Ca^{2+} release, driving inward Na^+ current via the NCX, leading to EAD and in particular DAD formation, which are important cellular arrhythmia mechanisms in AF, VT, and SCD.[21]

Reentrant Arrhythmia

In reentry, a group of myocardial cells that are not activated during the early stage of depolarization can resume excitability before the impulse vanishes. In this situation, they may connect to re-excite zones that were previously depolarized but were recovered from the refractory period of the initial wave. Two crucial factors predisposing reentry are prolonged conduction time and shortened refractory period. Reentry is the dominant mechanism of arrhythmias in the clinical setting and occurs due to anatomic and functional factors.[22]

Classification of Clinical Arrhythmias

Clinically, cardiac arrhythmias are usually classified as bradyarrhythmias and tachyarrhythmias (Figure 1). Both types can reduce cardiac output, resulting in hypotension and ultimately can cause death but have different underlying mechanisms. Figure 1 lists the major clinical types of brady and tachyarrhythmias. Briefly, bradyarrhythmias reduce the heart rate either by reducing spontaneous depolarization within the sinoatrial node, slowing conduction through the conduction system, or increasing parasympathetic tone. Sinus bradycardia, sinus node exit block, sinus arrest, and asystole are caused by dysfunction within the sinus node itself, due to destruction of the pacemaker cells, fibrosis of the sinoatrial node, or increased parasympathetic tone. AV nodal block prolongs the conduction above, within or below the AV node. Depending on the severity of AV block, it is classified as first-degree, second-degree, or complete (third-degree) heart block (Figure 1).

Tachyarrhythmias are accelerated rhythms that originate from either above (supraventricular tachycardia) or below the AV node (ventricular arrhythmia). The most common supraventricular tachycardias are sinus tachycardia and AF. Premature atrial contractions and AT are commonly caused by automatic foci within the atria. Reentrant atrial arrhythmias include atrial flutter, AV nodal reentry tachycardia, and AV reciprocating tachycardia. Atrial flutter is a macroreentrant loop, typically involving the tricuspid annulus limited by anatomic

barriers such as the superior and inferior cava veins, the coronary sinus and crista terminalis.[23] AV nodal reentry tachycardia is a microreentry related to differences in the refractory period of the slow and fast pathway within the AV node.[24] AV reciprocating tachycardia, also known as preexcitation syndrome, occurs due to the presence of an accessory pathway, most notably the Bundle of Kent leading to Wolf-Parkinson-White syndrome, which can prematurely conduct impulses between the atria and ventricles.

Ventricular arrhythmias include premature ventricular contractions (PVCs), VT, and VF. PVCs are single premature beats due to EADs or DADs in myocardial cells and benign, unless they trigger VT or VF. VT and VF are usually reentrant arrhythmias, and if not treated rapidly, can lead to sudden cardiac death. While a majority of cases of VT are because of reentry around the scar in structural heart disease, 10% of VT occurs in structurally normal hearts due to nonreentrant mechanisms such as catecholaminergic polymorphic VT (CPVT), fascicular VT, left or right outflow tract VT, mitral and tricuspid annular VT, long QT, and Brugada syndrome.[25]

Animal Models

An important consideration for selecting an animal model to study cardiac arrhythmias is how closely the species resembles human cardiac physiology. Caenorhabditis elegans and Drosophila melanogaster both develop heart tubes and have been primarily used to screen gene function and examine development and cardiac structure. Zebrafish have a 2 chambered heart with some similarities in AP electrophysiology to humans and provide advantages for understanding cardiogenesis. Zebrafish embryos are transparent, enabling optical viewing, fluorescent protein expression, and optogenetic pacing; they have large clutch sizes with a rapid embryonic stage lasting only 3 to 4 days postfertilization; are amenable to drug absorption; and genes are easily manipulated. Mouse hearts are anatomically similar to human hearts with 4 chambers and comparable development,[26] albeit differences in coronary anatomy.[27] However, there are major differences in heart rate, cardiac AP, and membrane currents (Figure 2). These differences influence ion channel function, refractoriness, and arrhythmia susceptibility. In addition, the small size of the mouse heart may contribute to the frequently observed self-termination of reentrant arrhythmias or lack of spontaneous arrhythmias in many models. Nevertheless, the mouse has been the primary animal model for cardiac arrhythmia studies of inherited cardiomyopathies and channelopathies, and many models faithfully capture cardiac disease. Rabbits more closely recapitulate the human AP compared with rats and mice. The rabbit AP has a sustained Ca^{2+} current-driven plateau phase, and the major repolarizing K^+ currents are similar to humans. Rabbit heart size and beating rate is between that of mice and humans. Dogs, pigs, and goats have a similar cardiac anatomy, size, and beating rate (slightly higher in dogs) as humans. Their cardiac electrophysiology, APs, and ionic currents are all fairly comparable to humans, and their primary limitations as an animal model for research come from their cost, size, and time to breed and reach sexual maturity.

ANIMAL MODELS OF GENETIC ARRHYTHMIA DISORDERS

Genetic arrhythmia disorders are either caused by or associated with identifiable gene mutations. Genetic arrhythmia syndromes can be subdivided into channelopathies without structural heart disease (eg, CPVT, long QT syndrome [LQTS], Brugada Syndrome) and genetic arrhythmia syndromes associated with structural heart disease (eg, hypertrophic cardiomyopathy [HCM], dilated cardiomyopathy [DCM], action potential duration [ARVC], AF). Tables 1 and 2 list published animal models of genetic arrhythmia syndromes. Most animal arrhythmia models are mice, given the ease of genetic manipulation. Despite differences between rodent and human cardiac electrophysiology (Figure 2), mouse models have enabled the study of human genetic diseases, identification of pathogenic mutations, characterization of disease pathophysiology, and testing/screening of therapeutic interventions. Advances in gene editing technology such as CRISPR/Cas9 have provided faster, easier, and cheaper methods to develop genetic models in animals and cells. Compared with cellular models such as human-induced pluripotent stem cells, animal models provide a distinct advantage in modeling cardiac arrhythmias where the anatomy of the heart is relevant.[217] In the following section, each of the major genetic arrhythmia syndromes are introduced, followed by examples of animal models that have informed disease pathophysiology and treatment approaches.

Channelopathies

Channelopathies are caused by mutations in ion channel genes or genes that regulate ion channels and generate arrhythmia risk in the structurally normal heart. However, overlap syndromes caused by mutations in channelopathy genes (eg, SCN5A) can also be associated with alterations in cardiac structure, which are discussed in Section genetic arrhythmia syndromes associated with structural heart disease.

Catecholaminergic Polymorphic Ventricular Tachycardia

CPVT is characterized by arrhythmogenesis evoked by elevated catecholamines during stress or exercise. CPVT is caused by gain-of-function mutations in proteins that constitute the intracellular Ca^{2+} release unit of the SR. These mutations result in spontaneous Ca^{2+}

Table 1. Animal Models of Genetic Arrhythmia Channelopathies

Disease, type, animal	Human ortholog gene (protein)	Mutation	Notes	Ref.
CPVT				
CPVT1				
Mouse	*RYR2* (RyR2)	R4496C±	Catecholamine/exercise-induced arrhythmia; phenotype not as penetrant as some other models	28
Mouse	*RYR2* (RyR2)	V2475F±	Homs are embryonic lethal, catecholamine-induced arrhythmia	29
Mouse	*RYR2* (RyR2)	R2474S±	Seizures, exercise-induced arrhythmia, sudden death	30
Mouse	*RYR2* (RyR2)	P2328S±	Iso-induced PVCs, VT, VF	31
Mouse	*RYR2* (RyR2)	R2474S/V3599K	GoF + LoF; protective- no arrhythmia	32
Mouse	*RYR2* (RyR2)	R4496C+/– with E4872Q+/–	GoF + LoF; protective- no arrhythmia	33
Mouse	*RYR2* (RyR2)	L433P+/–, N2386I+/–	Mutations from patients with CPVT; no report of CPVT in mouse models; mice also develop AF with pacing protocol	34
Mouse	*RYR2* (RyR2)	R176Q±	CPVT-like phenotype; AF	35
Mouse	*RYR2* (RyR2)	exon3del±	Homs embryonic lethal, hets did not develop CPVT; patients with exon3del have exercise-induced VT	36
C. elegans	*RYR2* (RyR2), *CASQ2* (Casq2)	R4743C, Casq2 KO	Enables optogenetic pacing, observed defect with mutations	37
CPVT2				
Mouse	*CASQ2* (Casq2)	KO	Severe CPVT, ultrastructure changes, catecholamine/exercise-induced arrhythmia	38
Mouse	*CASQ2* (Casq2)	D307H/D307H, D309deltaE9/D309deltaE9 (Casq2-/-)	Both mutations result in loss of Casq2 protein, catecholamine/exercise-induced arrhythmia	39
Mouse	*CASQ2* (Casq2)	Ventricular/Purkinje KO	Subtissue-selective knockout	40
Mouse	*CASQ2* (Casq2)	Ventricular/Purkinje KO	Subtissue-selective knockout	41
Mouse	*CASQ2* (Casq2)	R33Q/R33Q	Reduction of Casq2 protein, ultrastructure changes, arrhythmia	42
Mouse	*CASQ2* (Casq2)	K180R±	Autosomal dominant inheritance; iso-induced arrhythmias	43
CPVT4				
Zebrafish	*CALM* (CaM)	N53I and N97S	Increased iso-induced HR (indicated dominant negative effect)	44
Zebrafish	*CALM* (CaM)	E105A	Arrhythmias, tachycardia, altered RyR2 binding	45
CPVT5				
Mouse	*TRDN* (Triadin)	KO	Ultrastructure changes; iso-induced arrhythmias; overlap syndrome with LQT?	46
CPVT?				
Mouse	*KCNJ2* (Kir2.1)	R67Q+/–, cardiac-specific	Structurally normal heart, iso-induced VT, no LQT	47
CRDS				
Mouse	*RYR2* (RyR2)	A4860G±	VF with sympathetic stimulation, homs embryonic lethal	48
Mouse	*RYR2* (RyR2)	D4646A±	RyR2 Ca2+ release deficiency syndrome (CRDS); homs are embryonic lethal	49
LQTS				
LQT1				
Mouse	*KCNQ1* (Kv7.1)	KO	Deaf, shaker/waltzer phenotype; LQT	50
Mouse	*KCNQ1* (Kv7.1)	Truncated isoform, cardiac-specific overexpression	LQT, sinus node dysfunction, occasional AV block	51
Mouse	*KCNQ1* (Kv7.1)	A340V–/–	Homs have LQT, hets do with gene dose dependence; PVCs after feeding (linked to diabetes)	52
Rabbit	*KCNQ1* (Kv7.1)	Y315S cardiac-specific overexpression	LQT; sympathetic stimulation induces EADs and VT; rabbits die within 3 weeks of AV node ablation	53
LQT2				
Rabbit	*KCNH2* (Kv11.1/hERG)	G628S cardiac-specific overexpression	LQT, spontaneous PVT, sudden death; prolonged APD	53
Zebrafish	*KCNH2* (Kv11.1/hERG)	I462R, M521K	2:1 block (phenotype)	54
Zebrafish	*KCNH2* (Kv11.1/hERG)	I59S–/–	2:1 block (phenotype); prolonged APD; EADs	55

(*Continued*)

Table 1. Continued

Disease, type, animal	Human ortholog gene (protein)	Mutation	Notes	Ref.
Zebrafish	*KCNH2* (Kv11.1/hERG)	Morpholino KD of WT + expression of hERG ± mutants	Tested 40 pathogenic and 10 nonpathogenic hERG mutants in the zERG background	56
LQT3				
Mouse	*SCN5A* (Nav1.5)	ΔKPQ/+	1505–1507 deletion; prolonged QT/QTc; prominent T wave; prolonged APD; arrhythmias; sudden death	57
Mouse	*SCN5A* (Nav1.5)	ΔQKP/+	1507–1509 deletion; long QTc, wide QRS, AV block; spontaneous PVCs, VT, and VF with sudden death; no atrial arrhythmias	58
Mouse	*SCN5A* (Nav1.5)	N1325S cardiac-specific overexpression	LQT; arrhythmia; sudden death; also other non-LQT3 features like shorter PR and elevated heart rate	59
Mouse	*SCN5A* (Nav1.5)	1795insD	LQT and Brugada in family; homs embryonic lethal; sinus node dysfunction, conduction slowing, bradycardia, and LQT	60
Guinea pig	*SCN5A* (Nav1.5)	Cellular model, isolated cells tx	Isolated cardiomyocytes treated with anthopleurin; rescued by mexillitine	61
Minor types of LQTS				
Mouse	*ANK2* (Ankyrin-B)	KO	LQT with HR deceleration, sinus node dysfunction	62
Mouse	*ANK2* (Ankyrin-B)	±	Bradycardia, variable HR, slow conduction, AV dissociation, long QTc; iso/exercise-induced PVT & death	63
Mouse	*KCNA1* (Kv1.1)	N-term fragment overexpression	Long QTc; spontaneous PVC, couplets, ventricular tachycardia	64
Mouse	*KCNA5* (Kv1.5)	W461F cardiac-specific overexpression	Long QTc	65
Mouse	*KCNB1* (Kv2.1)	N216 cardiac-specific overexpression	Long QTc	66
Mouse	*KCND2* (Kv4.2)	W362F cardiac-specific overexpression	Subtle bradycardia, prolonged QTc	67
Mouse	KCND2×KCNA4	W362F×KO	QRS widening, prolonged QTc, AV block/dropped beats, spontaneous ventricular arrhythmia	68
Rabbit	*KCNE1* (minK)	G52R dominant negative overexpression	Long QTc; drug-induced arrhythmia (Torsades)	69
Mouse	*KCNE1* (minK)	KO	LQT with HR deceleration	70
Mouse	*KCNE2* (MiRP1)	KO	Long QTc with age, mice had hyperkalemia	71
Mouse	*KCNE3* (MiRP2)	KO	Females have long QTc at 9 mo (hyperaldosteronism); increased susceptibility to IR arrhythmias	72
Mouse	*KCNJ2* (Kir2.1)	KO	Bradycardia, LQT	73
Mouse	*KCNJ2* (Kir2.1)	T75R cardiac-specific overexpression	Long QTc; spontaneous VT; iso-induced PVCs, VT, atrial flutter/fibrillation	74
Mouse	*KCNIP2* (KChIP2)	KO	Significant reduction in Ito; elevated ST segment, atrial flutter and VT with PES; prolonged APD in cells	75
Mouse	*CACNA1C* (Cav1.2)	−/−, ±	KO embryonic lethal, hets survive and are just like WT	76
Mouse	*CACNA1C* (Cav1.2)	G406R cardiac-specific overexpression	Long QTc, exercise-induced PVCs and Torsades; crossing with AKAP150 KO protected against all phenotypes of the G406R mutant	77
Zebrafish	*CALM* (CaM)	D129G	Bradycardia; conduction abnormality; LQT	78
Mouse	*SCN1B* (Scn β1)	KO	Bradycardia, prolonged APD/QTc, slowed repolarization; sodium channel expression increased	79
Mouse	*SLC18A2* (VMAT2)	±	LQT	80
Mouse	*ATP1A3* (NaK ATPase α3)	Human isoform overexpression	LQT, steeper QT rate dependence, T wave alternans, VT	81
Short QT syndrome (SQTS)				
SQTS1				
Rabbit	*KCNH2* (Kv11.1/hERG)	N588K cardiac-specific overexpression	Shortened APs and QTc, normal T wave height, ex vivo perfused hearts inducible VT/VF	82
Zebrafish	*KCNH2* (Kv11.1/hERG)	L499P	SQT	83
SQTS8				
Zebrafish	*SLC4A3* (AE3)	Knockdown	SQT and systolic duration; WT SLC4A3 expression rescued phenotype, but R370H did not	84

(*Continued*)

Table 1. Continued

Disease, type, animal	Human ortholog gene (protein)	Mutation	Notes	Ref.
Mouse	*SLC8A1* (NCX)	KO	SQT	85
Mouse	*CAV3* (Caveolin 3)	WT cardiac-specific overexpression	Short QTc, bradycardia, prolonged PR	86
Kangaroo	Unknown	None reported	Kangaroos have LV hypertrophy, SQT, and are highly susceptible to VF and sudden death, especially under light anesthesia	87
BrS				
Pig	*SCN5A* (Nav1.5)	E558X±	Conduction abnormalities, QRS widening, reduced conduction velocity, ex vivo hearts have increased susceptibility to VF	237
Mouse	*SCN5A* (Nav1.5)	±	KO is embryonic lethal; hets have sick sinus, slowed conduction, pacing-induced VT; QTS widening and fibrosis with age	88
Mouse	*SCN5A* (Nav1.5)	1795insD	LQT and BrS in family; hom mice embryonic lethal; sinus node dysfunction, conduction slowing, bradycardia, and LQT	60
Mouse	*SCN5A* (Nav1.5)	ΔSIV/+	C-term truncation; SA, AV, and His conduction slowing; one human patient with V2016M diagnosed with Brugada	89

AF indicates atrial fibrillation; APD, action potential duration; AV, atrioventricular; caff, caffeine; BrS, Brugada Syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; CRDS, calcium release deficiency syndrome; DAD, delayed afterdepolarization; DKO, double knockout; DN, dominant negative; EAD, early afterdepolarization; GoF, gain of function; het, heterozygous; HF, heart failure; hom, homozygous; HR, heart rate; IR, ischemia-reperfusion; iso, isoproterenol; KO, knockout; LoF, loss of function; LQTS, long QT syndrome; MVT, monomorphic ventricular tachycardia; NSVT, nonsustained ventricular tachycardia; PES, programmed electrical stimulation; PVC, premature ventricular complex; PVT, polymorphic ventricular tachycardia; RBBB, right bundle branch block; SVT, supraventricular tachycardia; VF, ventricular fibrillation; and WT, wild type.

release from RYR2 SR Ca^{2+} release channels, raising diastolic Ca^{2+} and generating membrane depolarizations and delayed afterdepolarizations via Ca^{2+} extrusion through the electrogenic Na^{+}- Ca^{2+} exchanger. Pathological mutations in RYR2 make up more than half of identified CPVT cases and are inherited in an autosomal dominant fashion. Mutations in regulatory partners of RyR2 are rarer and include calsequestrin, calmodulin, and triadin. Evidence suggests that KCNJ2 mutations may also be involved in CPVT.

Mice have been the primary animal model for studying CPVT and have been valuable not only to establish arrhythmia pathophysiology but also to identify new drug therapy that proved efficacious in humans.[218] At least 1 attempt to generate a rabbit model overexpressing human RYR2-R4497C was unsuccessful, likely due to the selected promotor and size of the transgene.[219] The first animal model of CPVT generated was an RYR2-R4496C± knock-in mouse,[28] which had exercise- and catecholamine-inducible ventricular arrhythmias. Since then, several mouse models have been designed that carry RYR2 mutations identified from patients with CPVT (see Table 1). When loss-of-function mutations are combined with gain-of-function mutations, mice are protected from CPVT.[33] Identifying the pathogenicity of specific mutations is important because RYR2 mutations are implicated in several other arrhythmia disorders, as detailed below. Interestingly, a RYR2-exon3 deletion was identified in patients with a severe form of CPVT, but the corresponding mouse model failed to reproduce the CPVT phenotype.[36]

Cardiac calsequestrin (CASQ2) mutations are inherited in an autosomal recessive manner, leading to loss of function. Casq2 serves as a high-capacity Ca^{2+} buffer in the SR and regulates RYR2 gating. In the mouse, CASQ2 deletion causes a severe exercise- and/or catecholamine-induced arrhythmia phenotype consistent with patients lacking Casq2 expression. Observations from CASQ2 mouse models carrying mutations identified from patients show these commonly lead to loss of Casq2 expression in the heart. Recent evidence, however, suggests that Casq2 mutations could also be inherited in an autosomal dominant manner.[220] A knock-in mouse model expressing Casq2-K180R± reported catecholamine-induced arrhythmias validating this inheritance pattern.[221]

Triadin is another protein in the SR Ca^{2+} release unit where autosomal recessive inheritance has been reported in patients with CPVT. When triadin was knocked out in mice, they developed substantial ultrastructural changes in the junctional SR and reduced expression of proteins comprising the Ca^{2+} release unit, leading to catecholamine-inducible arrhythmias.[46] Calmodulin genes (CALM1/2/3) encode 3 identical proteins (CaM) and some mutations are associated with CPVT.[222] Zebrafish models have been generated to examine the pathogenesis of overexpressing CALM mutations, and they have successfully demonstrated cardiac arrhythmias (Table 1). Finally, KCNJ2 loss of function mutations, which commonly have been linked to the Anderson-Tawil Syndrome and cause reduced IK1 current (see section Long QT syndrome), have also been identified in patients with CPVT. A knock-in mouse carrying KCNJ2— R67Q± had significant evoked arrhythmias without any QT prolongation (Table 1).

The CASQ2 knockout (KO) mouse is an excellent model to investigate CPVT. It has a severe and highly penetrant phenotype, something not always observed

with RYR2 mouse models of CPVT (Table 1). The age of onset for CPVT is only a few weeks old and mice have spontaneous arrhythmias under normal housing conditions.[38] CASQ2 KO mice were used to establish proof of principle for the efficacy of gene-therapy in CPVT.[223] In what may be the only example of its kind for an arrhythmia syndrome, the CASQ2 KO mouse was used to establish the therapeutic efficacy of an existing FDA-approved drug, flecainide, in CPVT.[218] CASQ2 KO mice were instrumental to demonstrate that in vivo, RYR2 block is the principal mechanism of flecainide's antiarrhythmic action.[224] Since its discovery in CASQ2 KO mice, flecainide has become the standard of care for preventing arrhythmias in CPVT patients when beta-blockers are insufficient.[225,226]

CASQ2 KO mice have also recently been used to establish a novel tissue mechanism responsible for ventricular ectopy in CPVT (Figure 3). To determine the cellular origin of ventricular arrhythmias in CPVT, Blackwell et al[41] used conditional murine models with Casq2 expression only in ventricular myocardium or in the specialized conduction system, utilizing the contactin-2 promoter to drive Cre expression and control tissue-specific Casq2 expression. CPVT occurred when Casq2 was deleted in the ventricular myocardium but still expressed in the conduction system. Moreover, catecholamine challenge did not elicit any arrhythmias when Casq2 was deleted in the conduction system but still expressed in the ventricular myocardium. Additional experiments determined that the subendocardial ventricular myocardium juxtaposed to Purkinje fibers is the only cellular source for focal ventricular arrhythmias in CPVT. To understand why that was the case, in silico modeling demonstrated an intriguing phenomenon whereby subthreshold DADs in ventricular myocardium elicit full-blown APs in the conduction system to generate arrhythmias, identifying the Purkinje-myocardial junction as the tissue origin of ventricular ectopy in CPVT (Figure 3). This discovery could shape treatment and may be critical to our understanding of arrhythmogenesis in other ventricular arrhythmia syndromes where DADs are the cellular arrhythmia mechanism.

Calcium Release Deficiency Syndrome

Whereas RYR2 gain-of-function mutations have been associated with CPVT, arrhythmogenic cardiomyopathies, and AF, loss-of-function mutations in RYR2 can cause an arrhythmia syndrome recently termed Ca^{2+} release deficiency syndrome (CRDS).[49] In patients with CRDS, exercise stress tests do not provoke arrhythmias. Consequently, this syndrome can escape clinical diagnosis and often presents as sudden cardiac death. In CRDS, arrhythmias are thought to develop because of electrophysiological remodeling. Given the substantial number of benign RYR2 mutations observed, predicting pathogenicity without in vitro or in vivo examination is challenging. CRDS has only been recently described, but 1 knock-in mouse model was generated carrying the patient-specific RYR2-D4646A± mutant allele.[49] Exercise and catecholamine challenge did not invoke arrhythmias, as predicted. Importantly, this animal model enabled the authors to establish a burst pacing protocol that induced arrhythmias, supporting a possible new clinical diagnostic tool, which was recently confirmed in a clinical study. A previously reported loss-of-function mutation, RYR2-A4860G±, was identified in a patient with idiopathic VF and subsequently knocked-in to a mouse, but arrhythmias were not reported in vivo.[48] Ex vivo hearts did develop VF in response to isoproterenol but had no arrhythmias in the presence of the RyR2 agonist caffeine. These data hint that this RYR2 loss-of-function mutation may be part of the calcium release deficiency syndrome. Prior work on RYR2 has focused on gain-of-function mutations. CRDS is a relatively new syndrome and animal models provide an opportunity to advance our understanding of CRDS pathophysiology and determine the impact of loss-of-function mutations.

Long QT Syndrome

Congenital LQTS often presents as a multiorgan syndrome caused by mutations in proteins responsible for the repolarization of the heart and can cause seizures, syncope, arrhythmia, and sudden death. Alterations in repolarization manifest as prolongation of the AP and, consequently, the QT interval, predisposing the heart to EAD, DAD, and reentrant circuits. Ca^{2+}, Na^{+}, and many K^{+} channels play a role in cardiac repolarization; accordingly, the genes involved in this syndrome vary and LQTS can be inherited in autosomal dominant or recessive forms. LQTS is traditionally described as a distinct disease manifestation; however, long QT intervals are observed in many overlap syndromes (see Table 1). Approximately 80% of LQTS cases are caused by mutations in KCNQ1 or KCNH2, with SCN5A constituting 7% to 10% of cases.[227] It should be reiterated that the currents responsible for mouse and human repolarization are quite different (Figure 2), and mice are inadequate to model human disease involving mutations in delayed rectifier K^{+} channels (eg, LQT1, LQT2).

An aspect of understanding LQT pathogenesis is the observed sex differences in patients, such as QT interval, the onset of cardiac events, and sudden death.[228,229] Animal models allow for significant insight into these investigations since most in vitro models fail to capture the hormonal factors that influence development and regulation. It is noteworthy that sexual dimorphism in QT is not captured by mouse models and may require other animal models such as rabbits.[230,231] Estradiol treatment in ovariectomized rabbits led to prolongation of the QT interval and changes in proteins responsible for repolarization, whereas dihydrotestosterone did not.[232] Another study in rabbits recapitulated findings in patients showing that QT interval was more prolonged in females following treatment with erythromycin.[233]

LQT1 is caused by loss-of-function mutations in KCNQ1 (Kv7.1). Knockout of KCNQ1 in mice leads to characteristics of Jervell and Lange-Nielsen syndrome, causing deafness and prolonged QT interval.[50] Other models have examined distinct mutations with varying phenotypes; however, caution should be used when reviewing the mouse LQT1 literature. Rabbits are a much better model for examining human-like mechanisms of altered repolarization. However, only 1 transgenic rabbit model is reported, which carries cardiac-specific overexpression of KCNQ1-Y315S, leading to LQT and inducible EADs and VT with sympathetic stimulation.[53]

LQT2 is caused by loss-of-function mutations in KCNH2 (K_v11.1). In contrast to humans, KCNH2 contributes little to repolarization in mice (Figure 2). As such, mouse models are not realistic for modeling LQT2 and should not be used. A rabbit transgenic model was generated with cardiac-specific overexpression of KCNH2-G628S and developed LQT, spontaneous PVT, and sudden death. Arguably, the most interesting LQT2 model is the work in zebrafish.[56] In 1 study, the endogenous ortholog of hERG (zERG) was knocked down using morpholinos and then various hERG mutants were expressed in its place. The phenotype data (prolonged APD and/or 2:1 AV block) correctly identified 39/39 pathogenic mutants and 9/10 nonpathogenic polymorphisms. Further work using this model could establish the pathogenicity of other variants of uncertain significance.

LQT3 is caused by gain-of-function mutations in SCN5A (Nav1.5). Several mouse models have been generated that recapitulate the LQT phenotype. Both the SCN5A-ΔKPQ/+ and SCN5A-ΔQKP/+ mouse models report many characteristic phenotypes such as prolonged QT interval, a more pronounced T wave, prolonged APD, arrhythmias, and sudden death, which make them suitable for examining LQT3 mechanisms and pathogenesis.[57,58] A successful bench-to-bedside study, conducted in ventricular myocytes isolated from guinea pigs, demonstrated that mexiletine restored the APD in cells treated with the Na^+ channel inactivation inhibitor, anthopleurin.[61] Mexiletine is now used routinely in the treatment of patients with LQT3. In rare cases, patients have been identified linking LQTS with mutations in the beta accessory proteins for SCN5A. An SCN1B knockout mouse was generated and had long QT, bradycardia, and delayed repolarization[79]; interestingly, it was found that these mice had increased Na^+ channel expression. Nav1.5 channel gating was unaffected, but peak and persistent currents were increased in isolated cardiomyocytes.

Andersen-Tawil syndrome is a rare LQTS associated with physical abnormalities and hypokalemic periodic paralysis and is primarily caused by loss of function mutations in KCNJ2 (Kir2.1), resulting in reduced IK1 current. Neonatal (1 day old) KCNJ2 knockout mice were characterized by long QT and bradycardia, before dying from complete cleft palate and inability to feed.[73] A more useful arrhythmia phenotype—LQT and spontaneous VT—was observed in the KCNJ2-T75R cardiac-specific overexpression mouse model.[74]

The remaining LQTS types result from mutations in K^+ channels, Ca^{2+} channels, and key regulators of ion channel function (Table 1). The ankyrin-B syndrome is characterized as an overlap syndrome, with long QT, sinus node dysfunction, conduction abnormalities, exercise-induced arrhythmia, VF, and VT. The ankyrin-B knockout mouse demonstrated long QT and sinus node dysfunction[62]; however, a more severe and faithful phenotype was reported in heterozygous mice, capturing many of the same observations from humans.[63] KCNE1 knockout mice developed long QT, but only when heart rate deceleration occurred.[70] A transgenic rabbit model overexpressing dominant negative KCNE1-G52R developed long QT and increased susceptibility to drug-induced arrhythmia by accelerating IKs and IKr deactivation kinetics.[69] This model could be useful for examining the proarrhythmic liability of drugs. CACNA1C (Ca_v1.2) gain-of-function mutations cause LQTS that can be associated with extracardiac manifestations known as Timothy syndrome. In mice, CACNA1C knockout is embryonic lethal, but heterozygous mice survived without any cardiac phenotypes. Cardiac-specific overexpression of the G406R mutation in mice led to long QTc and exercise-induced PVCs and Torsades de Pointes (TdP).[77] It was hypothesized that this mutant had altered interaction with AKAP150; in fact, when G406R-overexpressing mice were crossed with AKAP150 KO mice, they were protected against all phenotypes of the G406R mutant.

Investigators have also knocked out many of the potassium channel genes in mice to determine their effects on cardiac electrophysiology. When a dominant-negative fragment of KCNA1 was expressed, mice developed LQT and spontaneous ventricular arrhythmias.[64] Interestingly, it was later shown by Glasscock et al[173] that KCNA1 is preferentially expressed (≈10-fold higher) in atria over ventricles. Programmed electrical stimulation (PES) induced AF in KCNA1 knockout mice but did not lead to any ventricular arrhythmias and no differences in QT interval were observed. Dominant negative overexpression of KCNA5, KCNB1, or KCND2 all prolonged the QT interval without any other overt electrophysiological changes. Mice do not express KCNE3 in the adult heart, but deletion led to long QTc in aged female mice because of hyperaldosteronism.[72]

Mouse models of LQTS should be viewed with caution when the repolarizing current of interest does not reflect the human AP. As transgenic rabbit models become more common, they may find strong ground in advancing our understanding LQT pathogenesis. Rabbits accurately capture sex differences and express a similar repolarization ion channel gene profile as humans. An area of value will be evaluating predisposition to drug-induced LQT and arrhythmia,[234] which rabbit models will be best suited to answer.

Short QT Syndrome

Short QT syndrome (SQTS) is an extremely rare disorder; only a few 100 cases have been identified to date. SQTS is caused by the shortening of the cardiac AP. Like long QT syndrome, alterations in cardiac repolarization alter the QT interval. Because of the abbreviated QT interval, the refractory period is also shortened, leaving the heart susceptible to reentrant arrhythmias. Symptoms associated with short QT syndrome include both atrial and ventricular fibrillation, palpitations, and sudden cardiac death. Gain-of-function mutations in KCNH2, KCNQ1, and KCNJ2 or loss-of-function mutations in CACNA1C, CACNB2, CACNA2D1, SCN5A, and SLC4A3 have all been associated with SQTS.

There are few genetic animal models available to examine SQTS in vivo. Zebrafish carrying the KCNH2-L499P mutation have a shortened QT interval.[83] Knockdown of SLC4A3 in zebrafish led to a short QT interval that was rescued by expressing WT SLC4A3 but not by SLC4A3-R370H, identified from a patient with SQTS.[84] To appreciably capture the human cardiac AP, a rabbit model was engineered to overexpress KCNH2 carrying the N588K mutation.[82] Transgenic rabbits had shortened AP and QTc but a normal T wave height. Ex vivo perfused hearts had inducible VT and VF; this model is arguably the best available and, as discussed above, rabbit models more accurately typify human cardiac repolarization.

Brugada Syndrome

Brugada syndrome (BrS) is a disorder characterized by elevated ST segment, partial bundle branch block, arrhythmia, and sudden cardiac death. It is commonly caused by mutations in SCN5A; however, ≈20 genes are now associated with BrS. Brugada ECG patterns are sometimes observed in overlap syndromes, such as with long QT syndrome, as SCN5A mutations are associated with several arrhythmia disorders. In mice, SCN5A deletion is embryonic lethal, but heterozygous mice survived and developed slowed conduction, pacing-induced VT, and fibrosis with age.[88] Interestingly, the authors observed variability in phenotype penetrance that correlated with NaV1.5 expression levels.[235] A mouse model for an overlap syndrome of LQT and Brugada was generated to carry 1795insD in SCN5A.[60] Homozygous mice were embryonic lethal, but heterozygous mice developed sinus node dysfunction, slowed conduction, bradycardia, and QT prolongation. Interestingly, CaMKII-dependent phosphorylation of wild-type Nav1.5 appears to phenocopy this mouse model, as late current predominates at slower heart rates. Phosphomimetic and phosphoablation mouse models demonstrated that phosphorylation and oxidation modulate Nav1.5 current and susceptibility to arrhythmias.[137,236] A transgenic pig model was generated to better understand BrS disease mechanisms. Pigs were designed to carry the orthologous SCN5A-E558X/+ mutation identified in a patient diagnosed with BrS and developed conduction abnormalities and QRS widening but had no elevated ST segment, arrhythmias, or sudden death through 2 years of age.[237] However, ex vivo hearts had increased susceptibility to VF with programmed stimulation. One debate surrounding BrS is whether many of the associated genes cause BrS or simply increase susceptibility to developing BrS. SCN5A mutations have variable and incomplete penetrance and differing phenotypes. Moreover, SCN5A mutations are prevalent in the general population and discerning pathogenesis can be difficult. Given the failure of animal BrS models to reproduce the full clinical syndrome, their utility studying BrS pathogenesis and treatment options remains to be determined.

Genetic Arrhythmia Syndromes Associated With Structural Heart Disease

Animal models have been beneficial for understanding the pathogenesis of arrhythmias caused by mutations in nonion channel genes that result in structural heart disease. The section below discusses the major arrhythmia syndromes associated with a cardiomyopathy phenotype (ARVC, HCM, and DCM) and microscopic structural disease such as AF, sick sinus syndrome, heart block, and preexcitation syndromes.

Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

ARVC/dysplasia is a disease manifesting as fibrofatty replacement of the right ventricular myocardium and widespread electrophysiological remodeling, predisposing individuals to ventricular arrhythmias and increased risk of sudden death. Approximately half of the ARVC cases are caused by mutations in desmosomal proteins, which make up cell-cell mechanical junctions. Arrhythmias often arise during periods of exercise or stress, suggesting that catecholamines contribute to arrhythmogenesis. Accordingly, one of the primary phenotypes in animal models is catecholamine-induced ventricular arrhythmias.

The primary genetic model used to study ARVC has been the mouse. Of note, mice do not get fatty infiltration in the heart, one of the primary phenotypes of ARVC in humans. However, numerous cardiac phenotypes have been found, from remodeling to arrhythmogenesis. The first genetic mouse models to examine the importance of desmosomal proteins were congenital knockouts (Table 2). Mouse models with global knockout of plakoglobin, desmoplakin, plakophilin-2, and desmoglein-2 are all embryonic lethal. However, heterozygotes survived and developed varying degrees of fibrosis and arrhythmia phenotypes (Table 2). Subsequent animal models were based on patient mutations and frequently resulted in haploinsufficiency. This seems to be the primary cause, along with repression of the Wnt signaling pathway. DSC2 (desmocollin-2) mutations are rare, and the link between

pathogenesis and this protein is not well understood because data are lacking and conflicting. DSC2 knockout mice are viable but did not develop any cardiac phenotypes. However, DSC2 knockdown reportedly led to altered ultrastructure and contractile dysfunction, while overexpression also led to fibrotic remodeling.[105] Germline knockout of DSG2 (desmoglein-2) results in embryonic lethality in mice, but the cardiac-specific knockout led to dilation, fibrosis, and electrophysiological remodeling. Finally, the inhibitor of apoptosis-stimulating protein of p53 has been linked to ARVC; knockout mouse model developed dilation, arrhythmia, and sudden death.[110]

The PKP2 (plakophilin-2) mouse model is well-suited for understanding ARVC mechanisms and disease progression. Heterozygote PKP2 mice survived and developed arrhythmias in the absence of overt structural remodeling,[98] which was validated in mice carrying a PKP2 truncation mutant.[99] These findings raised an interesting question about the cause of arrhythmias: how do arrhythmias arise in the absence of structural changes to the heart? Because PKP2 knockout is embryonic lethal, a cardiac-specific inducible PKP2 knockout mouse was generated, which had many of the characteristic ARVC phenotypes: fibrosis, remodeling, reduced ejection fraction, arrhythmia, and sudden death.[100] In this model, PKP2 signaling regulates transcription of many genes involved in Ca^{2+} homeostasis and proteins of the intracellular Ca^{2+} release unit are downregulated, causing proarrhythmic RyR2 activity. The authors discovered that flecainide, a class Ic antiarrhythmic that inhibits RyR2 channels, effectively prevented arrhythmias in these mice. Exercise exacerbated RyR2 hyperactivity, and it was shown that membrane-permeable beta-blockers had greater efficacy than nonpermeable beta-blockers.[238]

ARVC has been observed in dogs and cats, generally of unknown cause. In these models, fibro-fatty replacement is commonly observed alongside syncope, arrhythmias, and sudden death. Dog models could be considered when disease mechanisms, as they relate to human cardiac (electro)physiology, are essential. Nondesmosomal proteins, such as phospholamban, RyR2, lamin A/C, transmembrane protein 43, and integrin linked kinase have all been associated with ARVC in patients; however, their role is less well understood due to the spectrum of phenotypes in ARVC. For example, some mutations in phospholamban cause DCM, which is a differential diagnosis, but may also present with ARVC. Because of the difficulty of identifying pathogenic mutations, diagnostic criteria rely on interpreting cardiac imaging and ECG data. An important line of investigation is understanding the molecular mechanisms that drive the development of the disease, as early disease progression escapes detection and the heterogeneity of genes involved makes prognosticating a diagnosis difficult.

Dilated Cardiomyopathy

Congenital DCM is characterized by ventricular dilation and is commonly caused by mutations in cytoskeletal or myofibrillar proteins leading to remodeling, reduced ejection fraction, conduction abnormalities, arrhythmia, and sudden death. Many animal models have been created to investigate the structural and functional consequences of these mutations. Here we focus on animal models where arrhythmias are a prominent feature of the reported phenotype (Table 2). Of note, there is significant overlap with the clinical diagnosis of arrhythmogenic (right ventricular) cardiomyopathy.

A widely studied DCM mutant is SCN5A-D1275N. A wide spectrum of phenotypes in different families carrying this mutation have been reported, including AF, conduction defects, and sinus dysrhythmia.[239,240] It is speculated that the variation in genetic background between the families contributes to these phenotypes. Homozygous SCN5A-D1275N mice developed many of the characteristic arrhythmia phenotypes observed in humans, while heterozygous mice did not.[138] Many changes in the ECG parameters reflected a gene dose-dependent effect and these features were also observed in zebrafish.[139]

Mutations in LMNA cause severe DCM and sudden death. Several mouse models have been generated that carry mutations identified from patients (Table 2). A variety of symptoms have been reported and spontaneous arrhythmias occur frequently. Mutations in RMB20 also have a severe phenotype in mice, commonly leading to spontaneous ventricular arrhythmias and sudden death. Duchenne muscular dystrophy has been studied in pig, dog, and mouse models, each having electrophysiological changes (Table 2).

Hypertrophic Cardiomyopathy

HCM is characterized by enlargement of the left ventricle primarily caused by mutations in sarcomeric proteins, leading to increased risk of arrhythmia and sudden death.[241] HCM is commonly caused by mutations in either the beta myosin heavy chain or myosin binding protein C, together accounting for nearly half of all cases. Mice express beta myosin heavy chain during cardiogenesis, but rapidly switch from the beta to the alpha isoform, postnatal. Numerous HCM animal models have been generated; however, the predominant focus has been the study of underlying changes in sarcomere function, contractility, and hypertrophy, without detailed examination of electrophysiological phenotypes. Many studies have reported on arrhythmia susceptibility in ex vivo hearts but only reports examining in vivo arrhythmia phenotypes are discussed here.

Alpha myosin heavy chain mutations are commonly associated with HCM, but the only reports of arrhythmias in an animal model come from the R403Q mutant, which was identified in MYH7 from a human patient. The knock-in mouse model was designed to carry R403Q in MYH6.[155] Mice developed HCM but only had a modest arrhythmia phenotype. A rabbit model was generated to overexpress the transgene but did not exhibit an arrhythmia phenotype.[242] Troponin mutations are also associated

with HCM and a transgenic mouse was generated to carry TNNI3-G203S.[153] Mice had conduction defects, but no other arrhythmias. However, when these mice were crossed with MYH6-R403Q mice, they developed a more severe phenotype with conduction defects, LQT, and catecholamine-induced VT.[154] Knockout of MYBPC caused long QT and spontaneous VT in mice.[158]

Several troponin T models have been designed to carry mutations identified in patients. Knollmann et al[149] showed that TNNT2-I79N mice had tachycardia, isoproterenol-inducible ectopy, and spontaneous nonsustained VT, despite having no hypertrophy or fibrosis. Subsequent work in mice demonstrated that Ca^{2+}-sensitizing TNNT2 mutations cause inducible arrhythmias, whereas nonsensitizing mutants (R278C) do not leave the heart susceptible to arrhythmias.[151] Myofilament Ca^{2+} sensitization increases cytosolic Ca^{2+}-binding affinity, alters intracellular Ca^{2+} homeostasis, and causes pause-dependent Ca^{2+}-triggered arrhythmia.[243] In addition, myofilament Ca^{2+} sensitization causes focal energy deprivation, which further increases arrhythmia susceptibility in mice.[244] Hence, myofilament sensitization per se, caused by drugs, mutations, or posttranslational modifications after myocardial infarction,[245] is a novel arrhythmia mechanism.[246] These reports illustrate the power of murine HCM models for discovering new arrhythmia mechanisms and identifying therapeutic targets.

Atrial Fibrillation

AF is the most common arrhythmia and is characterized by rapid, abnormal atrial rhythms, with symptoms manifesting as palpitations, syncope, stroke, and heart failure, among others. The etiology of AF is multifactorial, stemming from environmental factors, diet, lifestyle, family history, medication, and surgery. For an in-depth review of acquired AF and various animal models available, the reader is referred to this review.[247] Many genetic animal models develop AF alongside their primary disease phenotype (see Tables 1 and 2), but the models discussed in this section are more directly related to AF as a primary pathology.

One trigger for AF is thought to be hypersensitive and leaky RyR2 channels. Thus, animal models of CPVT (both gain-of-function RyR2 and loss-of-function Casq2) have been used to investigate arrhythmogenic mechanisms and screen therapeutic modalities.[165] It was demonstrated that RyR2 inhibition can attenuate AF in these models. Other CPVT models are susceptible to AF with PES. A more severe phenotype was seen with CREM mice, which developed atrial dilation and spontaneous paroxysmal and persistent AF that worsened with age.[167] A second trigger for AF may be channelopathies that accentuate excitability. KCNE1, SCN5A, KCNQ1, SK2, and SK3 mutations have all been introduced into mice, with varying phenotypes (Table 2). The KCNE1 knockout mouse develops spontaneous AF.[172] SCN5A models show overt structural changes, fibrosis, conduction abnormalities, and mitochondrial injury. Proteins associated with development, signaling pathways, and transcription regulation have been found to induce AF. Atrial-specific or complete knockout of LKB1 in mice caused electrical and structural remodeling and mice developed spontaneous AF.[179,180] A goat model overexpressing constitutively active TGF-β1 had atrial fibrosis and AF inducibility with PES.[181]

Genome-wide association studies have identified many gene loci associated with increased AF risk.[248] AF loci include genes known to affect ion channel function, cardiogenesis, or cell-cell conduction, although in many cases, candidate genes have not been determined. There are several animal models of inherited AF, mostly in mice. A primary challenge with mouse models of AF is that they do not commonly develop spontaneous AF, instead, only uncovering the phenotype with PES. Moreover, AF typically lasts for a brief period (on the order of seconds) before resolving. However, some mouse models have more severe and protracted AF that occurs spontaneously (Table 2). AF manifests in a wide range of cardiac diseases and resolving causative versus correlative pathogenesis is ongoing for some genetic models. Despite these shortcomings, investigators have successfully captured AF phenotypes in many different mouse models for genes identified in genome-wide association studies studies or laboratory testing.

Genome-wide association studies have identified loss of function (PITX2, TBX5, GJA1) and gain of function (KCNN3) variants associated with patients with AF. PITX2 heterozygous mice had normal cardiac parameters except reduced transpulmonary flow; however, ex vivo hearts were more susceptible to atrial pacing-induced arrhythmia.[176] Subsequent work showed AF in vivo with PES and several groups have used this model to study AF and explore treatment,[249] especially since PITX2 is the most common risk locus identified in patients with AF. Inducible deletion of the TBX5 transcription factor led to a much more severe phenotype of spontaneous AF and electrophysiological remodeling within 2 weeks of tamoxifen treatment.[177] Gene profiling identified numerous changes in the expression of Ca^{2+} handling proteins and ion channels, including PITX2. These data provide a link between TBX5-PITX2 activity and electrophysiological protein regulation in the heart. AF may also be promoted by delayed conduction. Mice carrying the GJA1-G60S/+ mutation are more susceptible to pacing-induced AF.[178] Mice overexpressing KCNN3 had bradyarrhythmias, heart block, abnormal AV node morphology, and sudden death.[212]

Many other models have explored mutations or deletion of other ion channels, transcription factors,

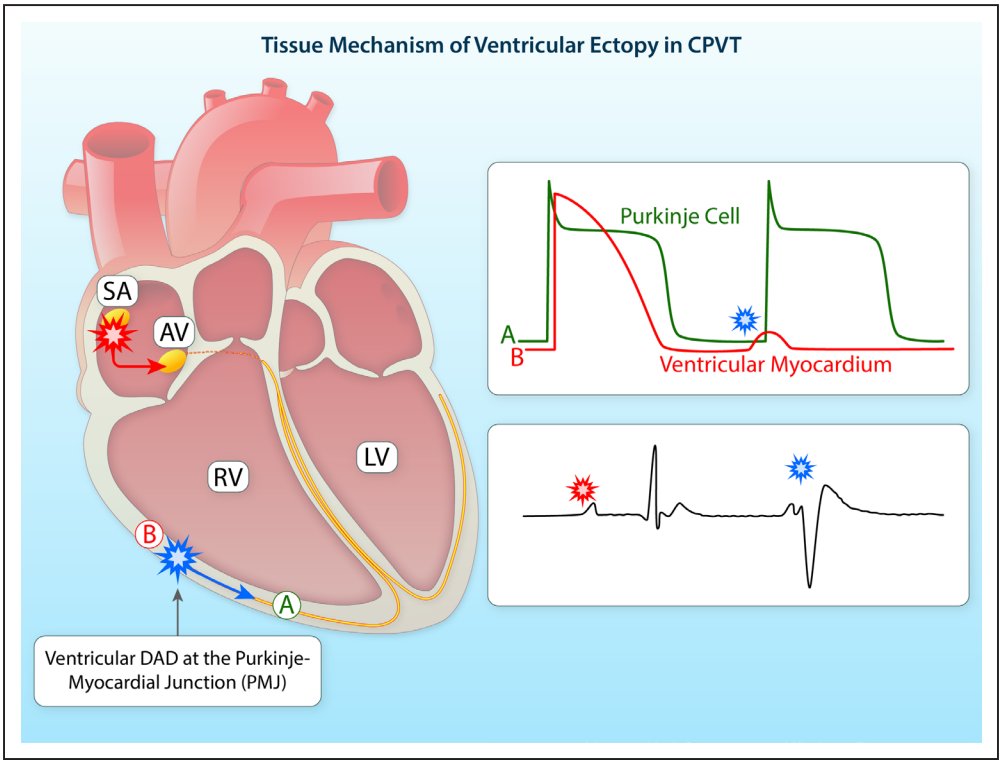

Figure 3. Tissue-targeted CASQ2 knock-out mice help decipher the anatomic origin of ventricular ectopy in catecholaminergic polymorphic ventricular tachycardia (CPVT).
Based on a combination of tissue-targeting and in silico modeling, the PMJ was identified as the likely origin of ventricular ectopy in CPVT. DAD indicates delayed afterdepolarization; LV, left ventricular; PMJ, Purkinje myocardial junction; and RV, right ventricular. Illustration credit: Ben Smith.

developmental pathways, or hormones to examine AF (Table 2). Data from patients have frequently confirmed the downregulation of various proteins, providing yet another link to pathogenesis. AF is a complex multifactorial disease; each animal model is an opportunity to extend our understanding of this disease.

Sick Sinus Syndrome

Sick sinus syndrome occurs when the sinoatrial node is not capable of generating a normal rhythm. In heterozygous SCN5A± mice (see also Brugada Syndrome), investigators identified sick sinus syndrome phenotypes[186] and sex differences in sinoatrial node function with age.[250] The hyperpolarization-activated cyclic nucleotide-gated channels (HCN) play an essential role in generating spontaneous pacemaker activity. Various models have examined the deletion of HCN1-4. HCN4 is the most abundant isoform, and congenital deletion in mice is embryonic lethal. However, embryonic hearts had sinus bradycardia.[194] Inducible cardiac-specific knockout led to severe bradycardia, block, and sudden death within days.[197] Mice with germline deletion of HCN1 or HCN2 survived and developed sinus dysrhythmia.[192,193] Deletion of HCN3 did not lead to bradycardia or arrhythmia, but mice had subtle perturbations in their ECG morphology at lower heart rates.[251] Perhaps the most elegant and accurate mouse model of sick sinus syndrome is an inducible HCN4-specific cellular ablation mouse.[198] This model accurately captured many of the phenotypes observed in patients, such as fibrosis of nodal tissue, sinoatrial dysrhythmia, supraventricular tachycardia, VT, and sudden death.

Atrioventricular Block

AV block is partial or complete disruption of impulse propagation from the atria to the ventricles. As the single site for collating atrial depolarization and passing it to the ventricle, aberrant AV node function may prevent or delay sinus rhythm from conducting into the ventricle. The AV node makes up part of the conduction system and, as such, expresses many of the same ion channels and gap junctions as the sinoatrial node, bundle of His, and Purkinje cells. AV block is observed in many of the models described above. However, some genes seem to specifically alter AV node conduction and effect block without altering sinus node rhythm. The NKX2-5 gene appears to be definitely related to AV block in patients, and mouse models carrying 2 different mutations independently validated the role of this gene in disease progression.[199,200]

Preexcitation Syndrome

Preexcitation occurs when the ventricles are activated prematurely via an accessory pathway. The most common mouse models generated to study preexcitation syndrome have mutations in PRKAG2, a regulatory subunit of 5′ AMP-activated protein kinase.[204–206] Mutations

Table 2. Animal Models of Genetic Arrhythmia Syndromes With Structural Heart Disease

Disease, type, animal	Human ortholog gene (protein)	Mutation	Notes	Ref.
Arrhythmogenic right ventricular cardiomyopathy				
Desmosomal				
Mouse	*JUP* (Plakoglobin)	±	Homs embryonic lethal; hets develop arrhythmia, RV structure change, etc	90
Mouse	*JUP* (Plakoglobin)	c.2037-2038delTG	Truncated form, LoF, mortality, fibrosis	91
Mouse	*JUP* (Plakoglobin)	23654del2 overexpression	Repressed Wnt signaling; fibrosis, dysfunction, death	92
Zebrafish	*JUP* (Plakoglobin)	Knockdown	Smaller heart size, blood reflux between chambers, reduced heart rate	93
Zebrafish	*JUP* (Plakoglobin)	2057del2	Structural change, mortality	94
Mouse	*DSP* (Desmoplakin)	±	Homs are embryonic lethal; hets have fibrosis, dysfunction, arrhythmias; Wnt signaling implicated	95
Mouse	*DSP* (Desmoplakin)	Conduction-specific KO (HCN4)	Migrating atrial pacemakers, sinus rhythm dysfunction, all without cardiac remodeling	96
Mouse	*DSP* (Desmoplakin)	R2834H cardiac-specific overexpression	Cardiac fibrosis, other small changes, no dysplasia	97
Mouse	*PKP2* (Plakophilin 2)	±	Homs embryonic lethal; hets histologically normal, but electrical remodeling, ultrastructure changes, arrhythmia susceptibility	98
Mouse	*PKP2* (Plakophilin 2)	S329X cardiac-specific overexpression	Histologically normal, but electrical remodeling, ultrastructure changes, arrhythmia susceptibility	99
Mouse	*PKP2* (Plakophilin 2)	Inducible cardiac KO	Fibrosis, arrhythmia, remodeling, death, reduced lvEF	100
Mouse	*PKP2* (Plakophilin 2)	R735X AAV9-expression	RV dysfunction with exercise	101
Zebrafish	*PKP2* (Plakophilin 2)	Knockdown	Structural defects, signaling reduced	102
Zebrafish	*DSC2* (Desmocollin 2)	Knockdown	Altered ultrastructure, contractile dysfunction	103
Mouse	*DSC2* (Desmocollin 2)	G790del/G790del, +/G790del	No phenotype	104
Mouse	*DSC2* (Desmocollin 2)	WT overexpression	Necrosis, acute inflammation and patchy cardiac fibrotic remodeling	105
Mouse	*DSG2* (Desmoglein 2)	KO	Embryonic lethal	106
Mouse	*DSG2* (Desmoglein 2)	Cardiac-specific KO	Dilation, fibrosis, electrophysiological remodeling	107
Mouse	*DSG2* (Desmoglein 2)	N271S cardiac-specific overexpression	Biventricular dilatation; spontaneous ventricular arrhythmias, cardiac dysfunction, sudden death	108
Mouse	*DSG2* (Desmoglein 2)	Q558X	Fibrosis, decrease in desmosomal size and number, and reduced Wnt signaling	109
Mouse	*PPP1R13L* (IASPP)	KO	Inducible Ppp1r13l knockout mouse model, dilation, arrhythmia, sudden death	110
Mouse	*SORBS2* (ArgBP2)	KO	QRS widening, RBBB, spontaneous PVCs, NSVT, VT	111
Nondesmosomal				
Mouse	*RYR2* (RyR2)	R176Q±	Patients with R176Q also have T250M and present with ARVC; but mouse 176Q alone gives CPVT-like phenotype; no ARVC/D, but slight end-diastolic changes	35
Mouse	*RYR2* (RyR2)	Inducible cardiac-specific KO	Sinus bradycardia, block, ventricular tachycardia, sudden death	112
Mouse	*ITGB1* (Integrin β1)	Inducible cardiac specific KO	Beta1d isoform is reduced in ARVC patients; KO mice had iso/caff-inducible VT	113
Mouse	*TMEM43* (Luma)	S358L±	Fibro-fatty replacement, structural abnormalities, arrhythmia, sudden death	114
Mouse	*ILK* (ILK)	Cardiac-specific KO	Arrhythmia, sudden death; arrhythmogenic cardiomyopathy in some patients with missense mutations in ILK	115
Mouse	*RPSA* (LAMR1)	1031 bp insertion (spontaneous)	ARVC; conduction abnormalities (QRS widening); no examination of inducible arrhythmias	116
Unknown				
Dog	Unknown	Autosomal dominant inheritance	Boxers; fatty replacement of RV myocardium, ventricular arrhythmia, syncope, sudden death	117
Dog	Unknown	Unknown	Weimaraner; syncope, ventricular arrhythmias, and sudden death, with histopathologic fatty tissue infiltration	118
Dog	Unknown	Unknown	English bulldog	119

(*Continued*)

Table 2. Continued

Disease, type, animal	Human ortholog gene (protein)	Mutation	Notes	Ref.
Cat	Unknown	Unknown	SVT, VT, PVT, RBBB	120
Dilated cardiomyopathy (DCM)				
Mouse	*LMNA* (Lamin A/C)	±	DCM, arrhythmia	121
Mouse	*LMNA* (Lamin A/C)	H222P/H222P	Chamber dilation; slowed conduction, AV block, spontaneous PVCs	122
Mouse	*LMNA* (Lamin A/C)	N195K/N195K	Bradycardia, exit block, AV block, arrhythmia, sudden death	123
Mouse	*LMNA* (Lamin A/C)	G609G/G609G	Truncating splice variant; bradycardia, QRS widening, SA block, LQT	124
Pig	*LMNA* (Lamin A/C)	G609G/+	Bradycardia, SA block, short QTc; spontaneous PVT, 3rd degree block at death	125
Zebrafish	*DES* (Desmin)	KO or aggregating mutant	Embryonic tachycardia, arrhythmia; however, no reports of electrophysiological changes or arrhythmias in two independent KO mouse models	126
Mouse	*DES* (Desmin)	R349P±	Human R350P; DCM, ARVC; slowed conduction and AV block; spontaneous and induced atrial fibrillation, PVCs, and VT	127
Zebrafish	*ACTN2* (F-Actin)	Knockdown	DCM, bradycardia	128
Mouse	*LDB3* (ZASP)	S196L cardiac-specific overexpression	DCM, arrhythmia	129
Mouse	*CDH2* (Cadherin)	cardiac-specific KO	DCM, arrhythmia, conduction defects	130
Mouse	*LMOD2* (Leiomodin)	KO	DCM; LQT	131
Rat	*RMB20* (RMB20)	KO	DCM; QRS widening, AV block, susceptibility to arrhythmias with PES, sudden death	132
Mouse	*RMB20* (RMB20)	KO	DCM; slowed conduction, LQT; changes in ion channel and calcium-handling proteins; spontaneous calcium release in isolated cardiomyocytes	133
Mouse	*RMB20* (RMB20)	S637A/S637A	DCM; spontaneous AF, spontaneous VT/VF with syncope, sudden death; much more severe cardiomyopathy than KO	134
Mouse	*PLN* (Phospholamban)	R14del/R14del	Mice develop severe DCM; no arrhythmias in vivo; explanted hearts have induced ventricular arrhythmias	135
Mouse	*SCN5A* (Nav1.5)	Cardiac-specific knockdown	Slow conduction, sudden death	136
Mouse	*SCN5A* (Nav1.5)	S571E/S571E	Phosphomimetic CaMKII target; LV dilation; LQT, iso-induced PVCs and VT	137
Mouse	*SCN5A* (Nav1.5)	D1275N/+ or D1275N/D1275N	Homs have slow conduction, heart block, AF, VT, and DCM without significant fibrosis or myocyte disarray	138
Zebrafish	*SCN5A* (Nav1.5)	D1275N	Bradycardia, sinus pause, AV block, sudden death; no AF or VT observed	139
Pig	*DMD* (Dystrophin)	KO (exon52del)	Fibrosis, low voltage areas, and sudden death	140
Dog	*DMD* (Dystrophin)	X-linked DMD	Short PR interval, sinus arrest, spontaneous ventricular arrhythmias	141
Mouse	*DMD* (Dystrophin)	KO (mdx strain)	Tachycardia; short PR, QRS, and QTc	142
Mouse	*DMD* (Dystrophin)	KO (5cv strain)	Short PR interval, inducible VT	143
Mouse	*VCL* (Vinculin)	Cardiac-specific KO	Normal sinus rhythm, AV block, spontaneous PVT, sudden death (before onset of DCM phenotype)	144
Mouse	*VASP* (VASP)	Cardiac-specific overexpression	Bradycardia, AV block, sudden death	145
Mouse	*REST* (NRSF)	DN cardiac-specific overexpression	Prolonged PQ, AV block, spontaneous VT, sudden death (observed as VT/VF with asystole)	146
Dog	Unknown	Autosomal dominant	Doberman Pinscher, DCM with age, PVCs on Holter monitor	147
Dog	Unknown	X-linked recessive inheritance	Great Dane; DCM; AF	148
HCM				
Mouse	*TNNT2* (TnT)	I79N cardiac-specific	Elevated diastolic Ca with elevated HR; iso-inducible ectopy; spontaneous NSVT; no hypertrophy or fibrosis	149
Mouse	*TNNT2* (TnT)	+/ΔK210 and ΔK210/ΔK210	Cardiac enlargement; HF; TdP, VF, sudden death; homs worse than hets but both had phenotype	150
Mouse	*TNNT2* (TnT)	F110I, R278C, or slow skeletal isoform TG	Iso-induced PVCs and VT in mice with F110I or skeletal isoform; VT inducibility with PES in ex vivo hearts; R278C had no arrhythmias compared to control	151
Rat	*TNNT2* (TnT)	Trunc transgenic overexpression	VT, VF	152

(*Continued*)

Table 2. Continued

Disease, type, animal	Human ortholog gene (protein)	Mutation	Notes	Ref.
Mouse	*TNNI3* (TnI)	G203S cardiac-specific overexpression	PR prolongation, conduction delay; no arrhythmias, but later shown to have AF	153
Mouse	*TNNI3* (TnI)×*MYH6* (α-MHC)	G203S×R403Q	Bradycardia, slow conduction (PR and QRS), long QTc, catecholamine-induced VT	154
Mouse	*MYH6* (α-MHC)	R403Q/+	Right axis deviation, prolonged ventricular repolarization and prolonged sinus node recovery times; programmable VT more in males than females	155
Mouse	*MYH6* (α-MHC)	R403Q overexpression		156
Mouse	*MYPBC3* (MyBP-C)	trunc/trunc	Arrhythmias with PES	157
Mouse	*MYPBC3* (MyBP-C)	KO	Prolonged QTc, spontaneous PVCs and VT	158
Cat	*MYPBC3* (MyBP-C)	A31P	HCM	159
Cat	*MYPBC3* (MyBP-C)	R820W	HCM	160
Mouse	*HRAS* (H-Ras)	Cardiac-specific overexpression	Sinus arrest, idioventricular rhythm, VT, block, and AF; phenotype stronger and more penetrant in females	161
Mouse	*RYR2* (RyR2)	P1124L/P1124L	Mild HCM; bradycardia, iso/caff-induced VT	162
Mouse	*OBSCN* (Obscurin)	R4344Q/R4344Q	Tachycardia, spontaneous PVCs and VT; all without structural remodeling	163
Kangaroo	Unknown	Unknown	Kangaroos have LV hypertrophy, short QT intervals, and are highly susceptible to VF and sudden death, especially under light anesthesia	87
AF				
SR Calcium Release				
Mouse	*RYR2* (RyR2)	L433P+/– , N2386I+/–, R2474S±	Mutations from CPVT patients. Also develop AF with atrial PES	34
Mouse	*FKBP1B* (FKBP12.6)	KO	No ECG abnormalities or spontaneous arrhythmias; AF with PES	164
Mouse	*CASQ2* (Casq2)	KO	AF with PES	165
Mouse	*JPH2* (Junctophilin 2)	E169K/+ (non AF-associated A399S ctrl)	E169K identified in HCM family with AF; before hypertrophy- AF with PES only in E169K mice	166
Mouse	*CREM* (CREM)	IbΔC-X	Atrial dilation; 100% of mice developed paroxysmal and persistent AF with age	167
Mouse	*NLRP3* (NLRP3)	A350V/+	Constitutively active; normal conduction, spontaneous PACs, pacing-induced AF	168
Mouse	*SLN* (Sarcolipin)	KO	Cellular APD prolongation; atrial fibrosis; AF with age	169
Ion Channel				
Mouse	*SCN5A* (Nav1.5)	F1759A±	Atrial and ventricular enlargement, myofibril disarray, fibrosis and mitochondrial injury, and electrophysiological dysfunction	170
Mouse	*SCN5A* (Nav1.5)	ΔKPQ/+	Atrial enlargement; increased susceptibility to AF with PES	171
Mouse	*KCNE1* (minK)	KO	Spontaneous AF	172
Mouse	*KCNA1* (Kv1.1)	KO	AF with PES	173
Mouse	*KCNJ2* (Kir2.1)	T75R cardiac-specific overexpression	Long QTc; spontaneous VT; iso-induced PVCs, VT, atrial flutter/fibrillation	74
Mouse	*KCNE5* (MiRP4)	KO	Inducible PVCs, atrial arrhythmia, PVT	174
Mouse	*KCNN2* (KCa2.2)	–/– and ±	Sinus and AV node dysfunction, AF with PES	175
Structural				
Mouse	*PITX2* (PITX2)	±	Normal cardiac parameters except reduced transpulmonary flow (pulmonary valve narrowing), ex vivo hearts were more susceptible to atrial pacing-induced arrhythmia	176
Mouse	*TBX5* (TBX5)	KO, inducible	Spontaneous AF within 2 wk post-induction, substantial arrhythmogenesis and cardiac remodeling starting after 3 wk, calcium-handling protein expression changes	177
Mouse	*GJA1* (Cx43)	G60S/+	Highly susceptible to inducible AF	178
Mouse	*STK11IP* (LKB1)	KO	Spontaneous AF, AV block, atrial flutter, electrical and structural remodeling	179
Mouse	*STK11IP* (LKB1)	Inducible atrial-specific KO	Spontaneous AF	180

(*Continued*)

Table 2. Continued

Disease, type, animal	Human ortholog gene (protein)	Mutation	Notes	Ref.
Mouse	*CALCR* (calcitonin receptor)	KO	Atrial fibrosis, inducible AF	180
Goat	*TGFB1* (TGF-β1)	C33S cardiac-specific overexpression	Constitutively active TGF-beta; atrial fibrosis, prolonged P wave, AF inducible with PES, no spontaneous or persistent AF	181
Mouse	*TGFB1* (TGF-β1)	C33S cardiac-specific overexpression	Constitutively active TGF-beta; atrial fibrosis, atrial inducibility with PES	182
Mouse	*MAP2K4* (MKK4)	Atrial-specific KO	Regulator of TGF-beta; reduced P wave amplitude, spontaneous atrial tachycardia, polymorphic atrial beats, AF induced ex vivo with PES	183
Mouse	*ACE* (ACE)	Cardiac-restricted expression	Atrial enlargement, mild fibrosis; low QRS voltage, spontaneous AF, sudden death (escape rhythm preceded death in observed cases)	184
Mouse	*JDP2* (JDP2)	Cardiac-specific overexpression	QRS widening, AV block, spontaneous paroxysmal AF; atrial hypertrophy, fibrosis	185
Dog	Unknown	Unknown	Great Danes with DCM; AF	148
Sick sinus syndrome				
Mouse	*SCN5A* (Nav1.5)	±	Bradycardia, slowed conduction, exit block	186
Mouse	*SCN3B* (Scn β3)	KO	Bradycardia, sinus conduction slowing, exit block, AV block	187
Mouse	*NOTCH1* (notch receptor 1)	Inducible intracellular domain (Notch activation)	Bradycardia, sinus pauses, reduced conduction velocity; atrial arrhythmias with PES; Nkx2-5, Tbx2, Tbx5 expression altered	188
Zebrafish	*SMO* (smoothened)	Unreported, homozygous	Bradycardia, reduced spontaneous hyperpolarizing current	189
Mouse	*SLC8A1* (NCX)	Atrial-specific KO	Bradycardia, no P waves, junctional escape rhythm (His)	190
Zebrafish	*SLC8A1* (NCX)	Truncation	Embryonic lethal; embryos have atrial fibrillation/bradycardia/tachycardia; some VF but mostly silent ventricle; cardiac morphological defects	191
Mouse	*HCN1* (HCN1)	KO	Bradycardia, sinus dysrhythmia, prolonged SA node recovery time, increased SA conduction time, and recurrent sinus pauses	192
Mouse	*HCN2* (HCN2)	KO	Sinus dysrhythmia	193
Mouse	*HCN4* (HCN4)	KO	Global or cardiac HCN4−/− embryonic lethal, but embryos have sinus bradycardia, isolated cells have no spontaneous pacemaker activity	194
Mouse	*HCN4* (HCN4)	R669Q±	Homs embryonic lethal, but hets survive and develop SA exit block during exercise	195
Mouse	*HCN4* (HCN4)	573X inducible cardiac-specific overexpression	Bradycardia, but no dysrhythmia	196
Mouse	*HCN4* (HCN4)	Inducible cardiac-specific KO	Bradycardia, reduced iso response, AV block, sudden death	197
Mouse	*HCN4* (HCN4)	Inducible HCN4+ cell ablation	Nodal tissue fibrosis, bradycardia, exit block, SVT, VT, complete block, sudden death	198
Atrioventricular block (AV block)				
Mouse	*NKX2-5* (NKX2.5)	I183P cardiac-specific overexpression	PR prolongation, worsening AV block with age	199
Mouse	*NKX2-5* (NKX2.5)	R52G±	PR prolongation, AV node smaller, AV block	200
Mouse	*DMPK* (DMPK)	−/− and ±	PR prolongation as mice age, ± mice develop 1st degree block, −/− mice develop third-degree block	201
Mouse	*GJA5* (Cx40)	−/−	Conduction delay (first-degree block)	202
Mouse	*TRPM4* (TRPM4)	KO	AV block (prolonged PR and QRS widening), Wenckebach	203
Preexcitation syndrome				
Mouse	*PRKAG2* (AMPK γ2)	R302Q cardiac-specific overexpression	Hypertrophy, preexcitation, accessory pathway, QRS widening, and inducible reentrant arrhythmia	204
Mouse	*PRKAG2* (AMPK γ2)	N488I overexpression	Hypertrophy, sinus bradycardia, accessory pathway, preexcitation	205
Mouse	*PRKAG2* (AMPK γ2)	R531G cardiac-specific overexpression	Hypertrophy, impaired contractile function, and electrical conduction abnormalities	206
Mouse	*TBX2* (TBX2)	Cardiac-specific KO	Accessory pathway, preexcitation	207
Other cardiac conduction disorders				
Mouse	*GJA1* (Cx43)	D378stop cardiac-specific inducible	Conducting truncation; germline deletion die right after birth; inducible model die 16 days after tamoxifen; 2-3-fold QRS widening, BBB, spontaneous MVT/PVT/VF, sudden cardiac death	208

(*Continued*)

Table 2. Continued

Disease, type, animal	Human ortholog gene (protein)	Mutation	Notes	Ref.
Mouse	*MAP2K4* (MKK4)	Cardiac-specific KO	Reduced Cx43 expression; ~55% QRS widening, long QTc, VT with PES	209
Zebrafish	*KCNJ3* (Kir3.1)	N83H cardiac-specific overexpression	Atrial dilation; sinus arrest, sinus bradycardia, SA block, and AV block; patient mutations associated with AF	210
Mouse	*CACNA1D/G* (Cav1.3, Cav3.1)	CACNA1D KO or CACNA1D/CACNA1G DKO	Sinus bradycardia, slow conduction; DKO also had 3rd degree block, escape rhythms, spontaneous VT	211
Mouse	*KCNN3* (KCa2.3)	WT overexpression	Bradyarrhythmias, AV block, abnormal AV node, sudden death	212
Mouse	*IRX3* (IRX-1)	KO	His-Purkinje transcription factor; normal PR, wide QRS, notched R wave, block; spontaneous PVCs and VT; iso- and exercise-induced VT	213
Developmental				
Mouse	*TBX3* (TBX3)	KO	Ectopic atrial pacemakers	214
Mouse	*TBX5* (TBX5)	±	Hypoplasia, arrhythmias, see above in atrial fibrillation	215
Mouse	*MECP2* (MeCp2)	KO	X-linked; long QTc, QRS widening, pacing-inducible VT, asystole/sudden death; neuronal KO was similar	216

Models are separated by disease, listing the animal species, orthologous human gene and protein, mutation, notable arrhythmia phenotypes/findings, and reference. AF indicates atrial fibrillation; APD, action potential duration; AV, atrioventricular; caff, caffeine; DAD, delayed afterdepolarization; DKO, double knockout; DN, dominant negative; EAD, early afterdepolarization; GoF, gain of function; HCM, hypertrophic cardiomyopathy; het, heterozygous; HF, heart failure; hom, homozygous; HR, heart rate; IR, ischemia-reperfusion; iso, isoproterenol; KO, knockout; LoF, loss of function; MVT, monomorphic ventricular tachycardia; NSVT, nonsustained ventricular tachycardia; PES, programmed electrical stimulation; PVC, premature ventricular complex; PVT, polymorphic ventricular tachycardia; RBBB, right bundle branch block; SVT, supraventricular tachycardia; VF, ventricular fibrillation; and WT, wild type.

in the TBX2 transcription factor also led to the development of an accessory pathway in mice.[207]

ANIMAL MODELS OF ACQUIRED ARRHYTHMIA DISORDERS

Acquired heart disease is the most common cause of increased arrhythmia risk in humans. Acquired heart disease develops over the course of a person's life becasue of structural remodeling associated with hypertension,[293] coronary artery disease,[225] nonischemic cardiomyopathy,[294] primary and secondary valvular disease,[295] autoimmune rheumatic diseases,[294] and myocarditis.[296] Acute cardiac stress or injury leads to activation of specific cell signaling pathways,[297,298] mitochondrial dysfunction,[299,300] altered Ca^{2+} handling,[301–303] and a switch in metabolism[304] from fatty acid oxidation to glycolysis.[305] This leads to chronic changes in gene expression of trophic and mitotic factors, inflammation, and ultimately to myocyte hypertrophy and fibrosis. Pathological fibrosis is characterized by excessive proliferation of cardiac fibroblasts and ECM (extracellular matrix) protein deposition. Several key profibrotic factors have been identified, including TGF (transforming growth factor)-β, angiotensin II and aldosterone, which contribute to the development of cardiac fibrosis regardless of the underlying pathology.[306] However, the relative contribution of a distinct molecular pathway depends on the type and the degree of the initial cardiac injury. Various animal models have been developed to study aspects of these acute and chronic changes leading to arrhythmia risk and are discussed below (Table 3).

Transverse Aortic Constriction

The transverse aortic constriction (TAC) model mimics chronic hypertension or aortic stenosis by causing a stricture in the thoracic aorta.[252] Left ventricular and atrial pressure overload increases the wall tension leading to hypertrophy, chamber dilation, and fibrosis.[307,308] This can be done in various methods, including sutures,[252,253] inflatable cuffs[309] or intravascular stents.[258] Within hours of injury, myocyte hypertrophy is induced by activation of p38 MAP Kinase,[310] ERK1/2,[311] and PI3K/AKT signaling.[312] Increased TGF-β production due to cytokine[313] and adrenergic receptor activation[314,315] leads to fibroblast proliferation and collagen deposition. The renin-angiotensin-aldosterone system plays an important role in developing hypertrophy and arrhythmia, as treatment with ACE inhibitors[316] and spironolactone[317] reduces fibrosis and improving conduction velocity. This initially leads to ventricular hypertrophy, later followed by chamber dilation.[313] While recruitment of $Ly6C^{low}CXCR1^{+}$ macrophages has been found in the LV early after TAC,[318] there is histologically less inflammation in this model than in other cardiac injury models.[313] Notable in this model is the upregulation of NCX[319] and downregulation of SERCA2a in myocytes over time, which is also seen in explant human hearts with reduced ejection fraction. While restoring SERCA2 has shown promise in improving systolic dysfunction[320,321] and suppression of ventricular arrhythmias[322,323] in animal models, the CUPID2 trial in patients with human hearts with reduced ejection fraction showed neutral results.[324]

In mice with TAC, multiple investigators have shown an increase conduction time, AP duration, and AV nodal

Table 3. Animal Models of Acquired Arrhythmia Disorders

Animal	Notes	Ref.
Transverse aortic constriction		
Mouse	Severity of injury dependent on strain (BALB/c>C57BL/6>129S1/SvImJ) and sub-strain (C57BL/6Tac>C57BL/6NCrl>C57BL/6J). Model requires PES to induce in vivo arrhythmias	252–254
Rat	Develop spontaneous arrhythmias with catecholamine challenge	255
Guinea Pig	High mortality, develops catecholamine-induced arrhythmias	256
Rabbit	In vivo injury, but arrhythmia studies completed ex vivo with Langendorff system	257
Pig	Model of heart failure with preserved ejection fraction, no study of arrhythmias	258
Sheep	Model of heart failure with reduced ejection fraction, no study of arrhythmias	259
Myocardial ischemia		
Mouse	Single left coronary artery leads to variation in severity of injury. Model requires PES with catecholamine challenge to induced arrhythmias	260–262
Rat	Requires PES and catecholamine challenge to induce ventricular arrhythmias reliably but rare spontaneous arrhythmias	263
Rabbit	PES done as ex vivo in Langendorff system	264
Dog	Atrial ischemia extensive studied	265
Pig	High mortality due to poor collateral circulation, early spontaneous VT/VF during injury and late model of SCD	266
Sheep	High mortality with spontaneous ventricular arrhythmia	267
AV node ablation		
Rat	High mortality, particularly in male rats. Requires specialized surgical equipment and skill	268
Rabbit	Studied completed ex vivo in Langendorff system	269
Dog	Can be induced minimally invasively with low mortality	270,271
Sheep	Can be induced minimally invasively with low mortality, model of TdP	272
Chronic atrial pacing		
Rat	Model for AF	273
Rabbit	In vivo pacing, but PES studied completed ex vivo with Langendorff system	274
Dog	AF and spontaneous VT model, recapitulates tachycardia mediated cardiomyopathy	275
Pig	AF model, recapitulates tachycardia-mediated cardiomyopathy	276
Chronic ventricular pacing		
Mouse	Requires tethered or ex vivo pacing	277
Rat	Model tachycardia mediated cardiomyopathy with VF induction with rapid pacing	278,279
Dog	Recapitulates tachycardia-mediated cardiomyopathy, model of spontaneous AF and VT	280
Sheep	Recapitulates tachycardia mediated cardiomyopathy with reduced ejection fraction, no studies of arrhythmia	281
Pig		282
Inflammation		
Mouse	Strain-specific susceptibility. C3H/He and DBA/2 mice susceptible to viral myocarditits while C57BL/6 are protected. BALB/c susceptible to immunogen induced myocarditis while C57BL/6 more resistive	283,284
Rat	Model of AF, but nonphysiological induction of inflammation with talc	285
Guinea Pig		286
Dog		287
Sheep		288
Metabolic/drug-induced		
Mouse	Streptozotocin and DIO models well established, increased susceptibility to AF and VT with PES	289,290
Rat	Age-dependent fibrosis found in Fisher 344 rat strain, model of AF	291
Rabbit	Established model of clofilium-induced TdP	292

Representative list of animal models with reference to the method to their development. AF indicates atrial fibrillation; DIO, diet-induced obesity; PES, programmed electrical stimulation; SCD, sudden cardiac death; TdP, Torsades de Pointes; VF, ventricular fibrillation; and VT, ventricular tachycardia.

refractory period, QT prolongation with inducible atrial (50%–60%) and ventricular arrhythmias (40%–50%), but spontaneous arrhythmias in vivo are rare.[325–328] Redistribution of connexin-43 (Cx43) laterally away from intercalating disk has been purposed to explain, in part, the changes in conduction in this model.[327] Arrhythmia induction can be challenging in this model, which is likely due to variability in the extent of constriction postprocedure,[254] the length of time of injury before analysis, sex, and strain.[329–333] Care must be taken when comparing results from different injury protocols and strains in this model.

Similarly, rabbits, rats, and guinea swine develop ventricular hypertrophy and dilation after TAC, albeit over a more extended period (8 versus 4 weeks in mice)[334] and with a higher incidence of sudden cardiac death. Unlike the mouse model, rabbits[335–337] (aortic insufficiency with abdominal aortic constriction), rats,[322,326] and guinea pigs[338–340] develop spontaneous arrhythmias in response to catecholamine challenge. Similarly, these animals develop ventricular hypertrophy, chamber dilation and fibrosis after TAC, albeit over a more extended period (8 versus 4 weeks in mice)[334] and with a higher incidence of sudden cardiac death. AP prolongation is a hallmark in these models and is linked to increased I_{NaL} and I_{NCX} with reduced I_{CaL} responsiveness to β-adrenergic stimulus and increased CaMKII activity, which is seen in human heart failure myocytes.[341] Overall, these animals seem to represent a better model for arrhythmias than mice, albeit most studies use explanted heart in the Langendorff system.

Unlike small animals, no studies report an increase in arrhythmia in large animals with TAC. Ascending aortic constriction in pig and sheep has been described with polyester band[259] or an implanted inflatable cuff.[309,342] The swine model of TAC differs from other species as they tend to develop heart failure with preserved ejection fraction characterized by LV hypertrophy with diastolic dysfunction.[343–346] In contrast to pig, sheep develop cardiac dysfunction at 6 to 18 weeks post-TAC with elevated markers of ECM remodeling, chemokine production, and apoptosis,[347] but no study reported arrhythmia generation outside procedural effects.

Myocardial Ischemia

Acute and chronic myocardial ischemia is a major cause of ventricular arrhythmias in humans. During acute ischemic, myocytes are exposed to hypoxia, acidosis, increased extracellular K+, and intracellular Ca^2+0.348[349] Under ischemic conditions, cardiomyocyte mitochondria switch to glycolysis from fatty acid oxidation to maximize ATP production with limited oxygen supply.[350] In addition, hypoxia leads to reactive oxygen species production that further damages intracellular proteins and organelles.[351] Myocardial infarction occurs with myocyte apoptosis and replacement fibrosis if normal blood flow is not restored. This is a highly inflammatory model, with significant infiltration of $CD11b^+$ macrophages and upregulation of inflammatory cytokines (CCL2, TNF-α, and IL-10) after injury, leading to proinflammatory $Ly6c^{high}CCR2^+$ macrophages early, then pro-wound healing $Ly6c^{low}CXCR1^+$ chronically, which contribute to interstitial fibrosis in the border zone.[352] Chronically, myocardial fibrosis leads to conduction heterogeneity, a substrate for reentry arrhythmias.

In mice and rats, myocardial ischemia is induced surgically, either transiently by ischemia/reperfusion (I/R) injury[260,353] or complete occlusion by coronary artery ligation[261,354] or cryoinjury.[262,353,355] Unlike complete occlusion, I/R injury produces reversible ischemia that leads to significant myocardial dysfunction without widespread necrosis in the area at risk. Spontaneous ventricular arrhythmias are observed during the reperfusion phase.[260] However, spontaneous ventricular arrhythmias are rare after complete occlusion aside from isolated preventricular contractions (internal data). In addition, LV dysfunction leads to volume overload in the left atrium, causing fibrosis and susceptibility to AF.[356]

Atrial and ventricular arrhythmias can be induced universally in isolated explanted post-MI hearts, with the occurrence of VT (inducible in up to 90%–100% in mice), VF (inducible in up to 89% of rats), and AF (inducible in 73% of rats and 33% of mice).[357–363] In vivo ventricular arrhythmia induction is more difficult, requiring rapid pacing protocols[364–366] and a catecholamine challenge. Transvenous, pericardial, and transesophageal protocols have been described for AF and ventricular arrhythmia induction, with the occurrence of VT (20%–70% in mice and rats)[367] and AF (60%–90% in mice).[368] Electrophysiological study of isolated myocytes from acute and chronic infarcted hearts has shown both shortening of the myocardial effective refractory period and slowing of condition time in the left atria, infarct, and border zone.[357] The proposed mechanism for AF induction is reduced expression of Cx40, dephosphorylation of Cx40 and Cx43, and redistribution from the intercalated disc to the lateral cell membrane.[362]

Established models for rabbit myocardial ischemia focus extensively on ex vivo studies using Langendorf perfusion systems. After infarction, rabbit myocardium shows prolonged APD and Ca^{2+} transients ex vivo.[369] Unlike mice and rats, infarction in rabbits leads to delayed AV nodal conduction becaue of fibrosis and reduction in Cx40 expression but did not affect the ventricular effective refractory period.[370] No arrhythmia induction protocol was used in these studies.

Dog models focus on atrial ischemia and arrhythmias, with ~40% of animals developing AF.[371] Increased I_{NCX} current, spontaneous Ca^{2+} leak, and conduction heterogeneity were found in myocytes from the border zone of the atrial infarct, supporting both triggered and reentry as the mechanism in this model.[372] The use of beta-blocker (nadolol) and Ca^{2+} channel inhibitor (nifedipine) were more effective at suppressing atrial arrhythmia in this model than class Ic (flecainide) or class III (dofetilide) antiarrhythmic drugs.[373]

Pig myocardial ischemia models are well established as they are of similar size and physiology as humans. Ischemia can be induced by either transient intravascular occlusion of the coronary artery or chronic occlusion with an ameroid constructor.[374] Acutely, pig are exquisitely sensitive to ischemia because of lack of functional collaterals at baseline, which leads to significant procedural mortality from VF.[375] After chronic ischemia, SCD due to spontaneous ventricular arrhythmias occurs in ≈60% to 70% of animals by 3 months.[376,377] Myocytes in the remote zone from have a decreased rapid delayed rectifier K^+ current (I_{Kr}), altered Na^+-Ca^{2+} exchange current (I_{NCX}), and increases of late Na^+ current (I_{NaL}), Ca^{2+}-activated K^+ current [$I_{K(Ca)}$], and Ca^{2+}-activated Cl^- current [$I_{Cl(Ca}$)]. In addition, myocytes in the border zone show the same changes along with a decrease of L-type Ca^{2+} current (I_{CaL}), a decrease of inward rectifier K+ current (I_{K1}), and arrhythmogenic SR Ca^{2+} release-induced EADs and DADs.[378] These changes in the current lead to shortening of the APD in the border zone and prolonged APD in the remote region, setting up a substrate for both triggered and reentrant arrhythmias. Gene therapy with dominant-negative K^+ channel (KCNH2-G628S)[379] or Cx43[380] reduced VT induction by prolonging the ADP and effective refractory period in the border zone.

Complete Heart Block and AV Node Ablation

Complete heart block leads to AV dyssynchrony and bradycardia, which acutely causes reduced cardiac output and induces volume overload. Compensatory hemodynamic changes occur to improve cardiac function, including ventricular dilation, hypertrophy, and increased stroke volume but are not able to fully restore cardiac output.[381] While genetic models are available for primary complete heart block, secondary complete heart block, which is characterized by fibrosis and necrosis of the AV node, is more difficult to reproduce. Outside histological remodeling, little is known about the molecular changes associated with secondary complete heart block.

Given the size, mouse AV node is challenging to identify without immunostaining.[382] Genetic have generated to establish the important transcription factors and ion channels in the AV node (noted in the above section atrioventricular block). Interestingly, disruption of tissue resident macrophages in the AV node, by either knockout of Cx43 in these cells or by genetic ablation of macrophages using diphtheria toxin receptor/diphtheria treatment, lead to progressive AV conduction block.[383] While these resident macrophages were noted in human AV nodes, it unclear if the presence or absence in of these cells contribute to human disease.

Electrical needle AV nodal ablation in rats has been described, as it was noted that alcohol injection leads to either transient block or mortality based on the amount used.[268,384] This is a technically challenging model with variable success[384] and high early mortality because of bradycardia and ventricular arrhythmias, as only 6-month-old female rats survived past 3 days.[268] Regardless, the surviving rats recapitulated the cardiac remodeling in humans, with 80% showing spontaneous TdP at baseline which could be induced to sustained VT with PES and isoproterenol challenge.[268]

The dog model of AV ablation by transvenous catheter injection for formaldehyde has been well established and leads to compensated hypertrophy and QT prolongation.[270,271] This is due to APD prolongation in the setting of bradycardia, with ≈50% of animals developing spontaneous and 90% drug-induced TdP.[385] Chronically, this reduced I_{Ks} current and enhanced Ca^{2+} influx by NCX, leading to increased SR Ca^{2+} content,[386] which increases the risk for DADs.[387] In contrast, goats undergoing AV ablation did not show APD prolongation but led to increased PLB (phospholamban), Troponin-I and myosin light chain kinase by PKA and RyR2 by CaMKII, suggesting increased Ca^{2+} sensitivity in this model.[272]

Chronic Tachypacing

Overriding the normal conduction system has many deleterious effects but is often reversible. Rapid atrial heart rate or pacing can lead to tachycardia-mediated heart failure, and long-term RV pacing in humans can lead to ventricular dyssynchrony, reduced cardiac output, and heart failure.[381] Long-term pacing has been shown to be detrimental to LV, with significant wall motion abnormalities and perfusion defects in the inferior and apical walls without corresponding coronary disease.[388] Conversely, cardiac resynchronization therapy improves HF outcomes for patients with HF and left-bundle branch block.

RV pacing has been used as a model of nonischemic cardiomyopathy, developing significant systolic dysfunction. Long-term RV pacing in AV nodal ablated dogs show the same perfusion mismatches seen in humans and was associated with increased sympathetic innervation of the ventricles.[389] Overdrive RV pacing for 4 weeks in dogs can induce spontaneous ventricular arrhythmias and SCD in 25% of dogs.[390] Myocytes isolated from paced ventricles showed prolonged ADP with reduced I_{to} currents,[391] likely due in part to downregulation of Kv4.3[392] and increased $I_{Na,L}$ [393] in failing heart. In addition, Ca^{2+} transients showed reduced amplitude, slowed relaxation, and blunted frequency dependence due to reduction in SERCA2a and upregulation of NCX in failing myocytes.[394] Cardiac resynchronization therapy in this model was showed to normalization of APD, reduce the $I_{Na,L}$ current, and prevent the negative remodeling associated with heart failure in this model.[393,395,396] VF can be induced in pig by applying AC current to the RV, but using arrhythmic drugs to improve resuscitation was not seen.[397]

Ventricular pacing in dogs also leads to secondary atrial fibrosis, dilation, and reduced function as the LV fails, inducing AF.[398,399] As with rapid ventricular pacing, rapid atrial pacing leads to a reduction in the I_{to}, in addition to $I_{Ca,L}$ and I_{Ks} currents.[400] If pacing is stopped and

the animal is allowed to recover, the ion currents return to normal, but fibrosis remains, leading to persistent AF. Studying atrial cells from dogs undergoing both rapid atrial and ventricular pacing has shown the atrial ion channel expression in HF, AT, and HF with AT can be significantly different.[401] Upregulation of profibrotic miRNA has also been described in atrial paced dogs, providing a novel target to prevent atrial fibrosis and AF.[402,403]

In rabbits, rapid atrial pacing increases atrial fibrosis and TGF-β signaling, which can be attenuated with losartan.[274] AF can be induced in 40% of rabbits in this model. Atrial pacing leads to decrease KCNE1 KCNB2 expression, reduced I_{Ks}, and shortening the AERP.[404] This was thought to be due to microRNA-1 upregulation in the atria.

In sheep, natriuretic peptide release is found immediately after RV pacing, returning to normal after cessation.[281] In goats, chronic atrial pacing led to atrial dilation, with reduced PKA phosphorylation of PLB and increased CaMKII phosphorylation of RyR2, leading to reduced SR Ca^{2+} load.[272] While structural changes similar to humans with tachycardia mediated cardiomyopathy are seen, increased arrhythmogenesis has not been reported.

Given their small size, in vivo pacing is difficult in mice. Tethered epicardial pacing has been used to study AV dyssynchrony and synchrony in mice after I/R injury. Dyssynchrony leads to further deterioration of cardiac function and activation of p38, ERK1/2, JNK, and MSK1 and inhibition of the GSK3β pathways. This was reversed by resynchrony.[277] Recently, the development of fully implantable epicardial micro pacing technology may allow for longitudinal pacing studies.[405]

In rats, initiation of rapid atrial pacing leads to upregulation of multiple voltage-gated K^+ channels (Kv1.5, Kv4.2, and Kv4.3),[273] which contribute to repolarization by I_{Kr} and I_{To}. After 2 days of atrial pacing, AF can be induced in ≈20% of animals, with upregulation of associated AF genes (CASQ2, KCNJ2, and TGFB) and activation of the TGF-β and IL-6 pathways.[406] Rapid transesophageal pacing of the LV has been used to reliably induce VF to study the effects of medication for resuscitation.[407]

Inflammation

Myocardial inflammation is a known driver of atrial and ventricular arrhythmias.[408,409] Postprocedural arrhythmias are common after cardiothoracic surgery but, while they are usually self-limiting, they lead to prolonged hospital stays.[410] While there is usually a preexisting arrhythmogenic substrate due to the underlying disease, surgical scarring and inflammation further exacerbate the system, leading to arrhythmia. Large cohort studies have shown elevated proinflammatory cytokines associated with persistent AF, including CRP,[411–413] TNF-α, IL-1β, IL-6, and IL-10.[414,415] After surgery, there is an increase in both macrophages and neutrophils to the surgical site, with reactive oxygen species production from MPO (myeloperoxidase) activity.[416,417]

Inflammation because of myocarditis is more complex, and the course of the acute and chronic phase of the immune response is dependent on the underlying cause (infectious versus rheumatological). The cytokine profiles are found in viral and autoimmune myocarditis includes more proinflammatory monocyte infiltration and myocyte necrosis than postsurgical injury.[418] This leads to a multitude of ECG changes, including sinus tachycardia, widened QRS patterns, low voltage, prolonged QT, variable AV blocks, and diffuse ST-elevations.[419–421]

Sterile inflammation has been used to induce AF in dogs[287] and sheep.[288] Pericardial talc treatment of dog atria to induce sterile inflammation induced AF in ≈60% of dogs and was significantly reduced with topical steroids or NSAIDS.[287] In sheep, treatment with atorvastatin reduced hs-CRP, IL-6, and TNF-α expression, which improved the atrial effective refractory period at 72 hours.[288] While inflammatory myocarditis can be induced in rats[285] and guinea pigs,[422] no current reports on the arrhythmia potential are available.

Currently, there are 2 models of viral myocarditis due to exposure to coxsackievirus B3 (CVB3)[423] and encephalomyocarditis virus A (EMCV).[424] There are several issues with the viral myocarditis models in animals. First, of the viruses primarily associated with human myocarditis (parvovirus B19, herpes simplex 9 and coxsackievirus B3), only CVB3 is infectious to animals, with EMCV only rarely causing human disease newborns. Second, the CVB3 mouse model is highly inflammatory and more mimics childhood infections than the milder course in adults.[425] Third, only particular stains of mice are susceptible to viral infection. Regardless, C3H/He mice exposed to develop similar arrhythmias to humans (80% sinus arrest, 30% second or third-degree AV block, 30% PACs, 20% PVCs, and 10% VT).[426] Ex vivo electrophysiological studies showed no change to the APD, but mice exposed to CVB3 were hyperpolarized with slightly increased VERP.[427] EMCV exposed DBA/2 mice develop AV block in 40% of mice over 2 weeks, with two-thirds of those mice showing mononuclear cell infiltration and edema and another one-third showing necrosis of the conduction system.[428] No further electrophysiological studies were conducted.

Traditionally, myocarditis can be induced in mice by either immunizing with a cardiac structural peptide (myosin heavy chain [MHC-α] or cardiac troponin I)[283] or delivering primed dendritic cells pulsed with MHC-α.[284] Importantly, BALB/c mice are susceptible to peptide immunized myocarditis while C57BL/6 strains are resistant, from which a majority of transgenic lines are created.[429] MHC-α peptide-induced myocarditis showed significant immune cell infiltration, increased expression of both TNFα and INFγ, fibrosis and prolongation for the APD in ventricular myocytes, which all could be attenuated with atorvastatin.[285,422,430]

Ctla4$^{+/-}$ *Pdcd1*$^{-/-}$ mice spontaneously develop myocarditis, modeling immune checkpoint inhibitor–induced

myocarditis.[431] These mice succumb to progressive ventricular hypertrophy and SCD early. Progressive AV block and sinus arrest occurs in ~30% of transgenic mice, similar to arrhythmia seen in patient with immune checkpoint inhibitor–induced myocarditis. Further study using this model would greatly improve treatment for patient with adverse events after immune checkpoint inhibitor therapy.

Metabolic- and Drug-Induced Arrhythmia

Dietary and metabolic considerations also contribute to atrial arrhythmia development as there is a known association with BMI and diabetes in AF,[432,433] and incidence of paroxysmal AF is reduced after gastric bypass surgery.[434] Off-target drug effects lead to adverse clinical outcomes, particularly arrhythmias induction due to block of delayed rectifier K^+ channels, I_{Kr}, causing drug-induced long QT syndrome and TdP ventricular arrhythmias.

Streptozotocin-induced diabetic models have been developed for both mice and rats[435] and consistently shown prolonged APD, increased sympathetic innervations, and inflammation. Studies have shown this is likely due to production of advanced glycation end products (AGEs) in diabetes animals, but they are inconstant in the electrophysiological mechanisms.[436] Initial studies showed a reduction in the I_{to} current as the underlying cause of AF,[437–439] while others suggest changes in sinoatrial node connexin channel expression,[440,441] atrial myocyte Ca^{2+} handling proteins (TRPC1/6, RyR3)[442] and AV nodal ion channels (TRPC1, CASQ2, RYR2, and RYR3)[443] are involved. Diabetic mice and rats also have reduced K+ channel expression, leading to overall reduced K+ currents, which was dependent on glycosylation of CaMKII and activation PKC.[444] Further studies showed in the setting of hyperglycemia, mice had more diastolic calcium leak through RyR2, prolonged ADP90, ADP alternans, increased DADs, and frequent premature ventricular complex, which could be suppressed by genetic inhibition of CaMKII.[445] Blocking IL-1β activation of CaMKII in this model restores the APD to normal and suppresses VT induction in explanted hearts from diabetic mice.[446] These studies all provide a central role for CaMKII in regulating ion channel expression and function in hyperglycemia.

Diet-induced obesity has been shown to affect inflammation and gene expression in multiple disease models. Mice fed 3 months of a high-fat diet had a 15% increase in their QTc and increased I_{Ks} current than mice on a normal diet and developed a 10-fold increase in premature ventricular complex burden.[447] The increased I_{Ks} current was thought to be due to the reduced expression of voltage-gated K^+ channels. Diet-induced obesity mice were also found to have reduced $Na_V1.5$ expression and current, leading to reduced ADP and conduction velocity in the atrial and increased incidence of induced AF.[448] Diet-induced obesity rats over 8 weeks have increased expression of $Ca_V1.2$, HCN4, Kir2.1, RYR2, NCX, and SERCA2a in the LV, which may contribute to DADs and triggered PVCs.[449] Rabbits fed a high-fat diet had increased cardiac sympathetic innervation (as seen by increased GAP23 expression), prolonged ADP and increased I_{Ca}, which led to QTc prolongation and repolarization heterogeneity in the ventricle.[450] Isolated hearts were more susceptible to VT induction. While these studies highlight the important changes to ion channel expression animals due to a high-fat Western diet, further study is needed to linking these findings to humans.

A specific line of inbred rats (Fischer F344 at 20–24 months) develop age-dependent adverse cardiac remodeling, with males developing more cardiomyocyte hypertrophy, intestinal fibrosis, and systolic dysfunction and females with more cardiac hypertrophy and diastolic dysfunction.[451] Aged female Fischer F344 rats show enlarged atrial, fibrosis, and CD68+ monocyte infiltration, similar to human disease.[452] Both male and female Fischer 344 rats are more susceptible to AF induction by atrial pacing, with 80% of animals showing atrial arrhythmia.[452,453] These are the only models of spontaneous AF in aged animals and could provide important insight to mechanism and future therapies for AF in our aging population.

In rabbits treated with clofilium (K^+ channel blocker), 70% of animals develop TdP, which can be increased to 100% with the addition of α1 agonist methoxamine.[454] Blockade of CaMK (calmodulin kinase) or PKA in this model reduced pause-dependent VT that was independent of these kinases effect on L-type Ca^{2+} channel activity.[455] Interestingly, the dose-dependent CaMKII blockade did not change the QT interval, unlike the dose-dependent PKA blockade. Further study showed that blocking CaMKII reduced the ratio of the TU interval, which is likely more critical than the QT interval in the induction of pause-dependent VT.[456]

EMERGING ETIOLOGIES OF ARRHYTHMOGENESIS: OPPORTUNITY FOR ANIMAL MODELS

Cardiac electrophysiology is regulated not only by the amino acid sequence at the protein level but also by posttranslational modifications, micropeptides, epigenetics, long noncoding RNAs (lncRNA), micro RNAs (miRs), aging, and environmental factors. Unprecedented advances in sequencing technology, deep mutational scanning, and epigenetic and transcriptome mapping have highlighted several new areas of pathogenesis. A primary challenge with many of the ascribed changes is whether they directly cause disease or, rather, follow disease progression. Animal models have been generated to address this challenge and study new areas of arrhythmia biology, with a select few highlighted below.

In the past decade, micropeptides have been identified that were previously excluded during annotations of open reading frames due to their small size or position in the transcriptome. In the heart, functionally expressed

peptides include examples such as sarcolipin and dwarf open reading frame, which regulate SR Ca reuptake. Sarcolipin protein levels are decreased in humans with AF or heart failure[457] and the sarcolipin knockout mouse developed AF with age.[169] In mice with DCM, overexpression of dwarf open reading frame attenuated the heart failure phenotype, although arrhythmias were not examined.[458] The micropeptides apelin and elabela affect cardiogenesis, fibrosis, hypertrophy, and inotropic responses. Reduced apelin levels predicted major myocardial events and MI scar size in patients with a previous MI event.[458] Apelin knockout mice developed larger scars and increased mortality following MI, although arrhythmias were not described.[459] These findings establish the pathogenic role and therapeutic potential for micropeptides in the heart, but their impact on arrhythmogenesis remains to be examined.

Posttranslational modifications, primarily phosphorylation, are documented in many arrhythmias.[460] While phosphorylation by PKC, PKA, and CaMKII are the most studied mediators for changes in Na^+ channels,[137,236,461,462] Ca^{2+} channels,[463–465] K^+ channels,[466] NCX,[467] and RyR2,[468] conflicting data exist regarding the relative contribution of different phosphorylation sites to ion currents. Phosphomimetic and phosphoablation mouse models have been created to tease out the importance of each site to arrhythmogenesis.[137,463,469,470] In addition, posttranslational modification of signaling kinases themselves, including PKA[471] and CaMKII,[471] play a role in arrhythmia susceptibility in response to oxidative stress. Other posttranslational modifications are less well studied, and it remains to be determined whether these cause disease or are merely epiphenomena.

Epigenetic DNA modifications regulate protein expression. It is now recognized that many cardiovascular diseases are associated with epigenetic changes. For example, cardiac-specific deletion of HDAC1 and HDAC2 in mice led to dilated cardiomyopathy, arrhythmia, and premature death.[472] A family with a history of autosomal recessive DCM was later discovered to carry homozygous mutation in GATAD1.[473] In AF, epigenetics also contribute to risk as it relates to hypertension, obesity, age, and other factors.[474] Patients with persistent AF have genome-wide changes in DNA methylation,[475] and animal models could help elucidate the pathophysiology of these changes at the whole genome or protein level.

MiRs regulate gene expression by RNA complementation and silencing. In the heart, miRs control cardiogenesis and pathways to affect gene expression during development. Some miRs are muscle specific and may serve as macroregulators of ion channel expression. In disease, changes in many different miRs have been documented. In dogs with rapid pacing, nicotine administration reduced miR-133 and miR-590 levels and increased AF risk.[476] Atrial tachypacing in dogs and development of AF was also associated with changes in many miRs compared with control.[477] Dogs with ventricular tachypacing developed CHF and AF and miR-29b levels declined within the first 24 hours of pacing.[478] In zebrafish, miR-182 served as a TBX-5 effector and miR-182 upregulation led to block, tachycardia, and arrhythmias.[479] In mice, it was shown that miR-1 directly binds to the C-terminus of Kir2.1 and represses channel activity.[480] Moreover, a single nucleotide polymorphism in miR-1 identified from patients with AF did not suppress Kir2.1 channel activity and failed to rescue arrhythmia inducibility in miR-1 knockdown mice (whereas WT miR-1 did). Of most interest is the therapeutic potential for RNA regulation to reverse disease progression.

LncRNA regulates gene expression via several mechanisms and changes in lncRNA expression have been documented in a wide range of diseases. Altered expression of lncRNA has been observed in AF,[481] including altered regulation of PITX2.[482] Another study in rabbits with AF induced by atrial tachypacing purported a mechanism whereby lncRNA "sponges" up miR-328 to regulate CACNA1C.[483] Yet another report indicated changes in lncRNA in AF reduce expression of JP2 and RYR2.[484] These studies demonstrate additional mechanisms of regulation beyond controlling gene expression and open up the field to exciting new opportunities in arrhythmia research.

CONCLUSIONS

For decades, animal models have been an essential tool to study arrhythmia pathophysiology and therapeutic approaches. Recent work with genetic mouse models yielded a new diagnostic tool in CRDS, identified lifesaving drug therapies for CPVT, LQT3, and ARVC, identified pathogenic mechanisms, and advanced our understanding of arrhythmogenesis in ways that other models cannot. The broad availability of transgenic mouse models and the option to generate mice with cell-specific and/or time-dependent regulation of gene expression provides a significant advantage of the mouse over other small animal species. A major limitation is that their fast heart rate, small heart size, and differential ionic currents do not fully recapitulate human cardiac electrophysiology. While guinea pigs and rabbits can overcome some of these electrophysiological limitations, genetic manipulation is limited in these species. Large animal electrophysiological and hemodynamic parameters match humans more closely but can be prohibitively expensive. Regardless, large animals are useful for preclinical studies evaluating new drugs, gene therapy, and devices that necessitate large animal models before moving to humans. Here, we provide an in-depth review of existing animal models to help interpreting published arrhythmia mechanisms as well as planning future experimental studies investigating cardiac arrhythmia diseases.

ARTICLE INFORMATION

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