Information Learned from Animal Models of Atrial Fibrillation

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KEYWORDS

• Cardiac arrhythmia • Atrial fibrillation
• Animal model • Remodeling

Atrial fibrillation (AF) continues to be the most common arrhythmia encountered clinically and is responsible for significant morbidity and health care cost. Therapy for AF has advanced significantly in recent years, mainly because of a better understanding of arrhythmia mechanisms. Several experimental animal models have been designed to study the underlying triggers and substrates that promote and maintain AF (**Table 1**). The present work summarizes notable findings from these various models.

PATHOPHYSIOLOGY OF ATRIAL FIBRILLATION

Chronic AF can be classified into three subtypes: paroxysmal, persistent, and permanent. Paroxysmal AF refers to episodes that start and stop spontaneously, persistent AF is one that requires cardioversion for its termination, and permanent AF denotes one that resists cardioversion or reverts quickly in spite of cardioversion. AF requires a trigger for its initiation and a suitable electrophysiologic or structural substrate for its maintenance. Triggers include atrial premature beats, vagal stimulation, bradycardia, acute atrial stretch, and ischemia, among others.[1–3] Recently, AF initiation from premature beats originating in the pulmonary veins (PVs) has received attention because ablation techniques have been able to cure this AF.[4] The mechanism underlying the PV ectopy is still debated. Enhanced automaticity, triggered activity, and microreentry have all been proposed as potential mechanisms for these beats.

After triggers propagate into atrial myocardium, fibrillation is maintained by continuation of these trigger beats with breakdown of conduction (so-called ''fibrillatory conduction'') or by intra-atrial reentrant processes. Fibrillatory conduction occurs when a stimulus site is activating at a rate that cannot be sustained through the mass of tissue; thus, conduction breaks down distal to the initiating site (**Fig. 1**A). Therefore, even though the arrhythmia comes from an organized focal site, the macroscopic appearance is of fractionated inhomogeneous conduction.

Currently, the dominant mechanistic theory for reentry sustaining fibrillation is the spiral wave model. Unlike the traditional concept of reentry that requires two pathways with differing conduction and refractory properties and anatomic separation between the two pathways, spiral wave reentry depends on functional properties of the tissue. Excitation occurs in a vortex spinning around an excitable but unexcited core. Conduction velocity (CV) is determined by the curvature of the spiral; thus, CV is fastest at the periphery of the wave, where curvature is widest. CV slows as the curvature increases closer to the core, and conduction is nonexistent at the core of the spiral, where curvature is essentially infinite (see **Fig. 1**B). This is in contrast to the so-called ''leading circle''

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Table 1
Clinical paradigms in animal models of atrial fibrillation

Model	Autonomic Stimulation	Atrial Tachycardia		Heart Failure	Atrial Tachycardia and Heart Failure		Sterile Pericarditis	Aging
Species	Dogs	Goats	Dogs	Dogs	Dogs	Pigs	Dogs	Dogs
AF	Sustained	Sustained	↑ Inducibility	↑ Inducibility	↑ Inducibility	Sustained	↑ Inducibility	↑ Inducibility
Electrophysiologic remodeling								
Functional	↓ AP, ERP ↑ ERP dispersion	↓ ERP Ø ERP rate adapt ±↔ CV	↓ ERP Ø ERP rate adapt ±↔ CV	↑ APD, ERP ↔ CV	±↓ ERP ↓ CV	NYR	ERP CV	↓AP, ERP ↑ERP, dispersion ↓CV of APDs
Ion current densities	↑ IK, ACh (cholinergic) ↑ IKs, ICa(L) (adrenergic)	NYR	↓ Ito, ICa(L), INa Ø IKs, IKr, NCX ↑IK1, IKACh	↓Ito, ICa(L), IKs Ø ICa(T), IKr, IK1, IKur ↑ NCX	↓ ICa(L), ± ↓ Ito, IKs Ø NCX ↑ IK1	NYR	NYR	NYR
mRNA expression	NYR	NYR	↓KCND3, CACNA1C, SCN5A ↔KCNO1; KCNH2; KCNJ2, 3, 5; SLCSA1	NYR	NYR	NYR	NYR	NYR
Protein expression	NYR	NYR	↓Kv4.3, Nav1.5 ↔Kir3.1, Kir3.4, NCX	NYR	NYR	NYR	NYR	NYR

Structural remodeling								
Anatomic	Normal	↑ Atrial size + Hypertrophy, myolysis, glycogen accumulation Fibrosis or apoptosis	↑ Atrial size Ø Fibrosis or hypertrophy	↑ A and V size + Fibrosis, hypertrophy	↑ A and V size	↑ A and V size + Fibrosis or apoptosis, inflammation, hypertrophy, myolysis	Epicardial: Apoptosis, inflammation, necrosis	+ Fibrosis
mRNA expression	NYR	NYR	↔ ECM	↑ Collagen, fibrillin-1, MMP2, TGFβ1, α-SM actin	NYR	↑ Fibronectin-1, fibrillin-1, fibromodulin, MLC-2v, collagen	NYR	NYR
Protein expression	NYR	↑ α-SM actin ↓ Cx40, titin cardiotin, desmin	↔ ECM	↑ Collagen, fibrillin-1, MMP2	NYR	↑ Fibronectin-1, fibrillin-1, MLC-2v fibromodulin, collagen	Epicardial: ↑ Vimentin ↓ α-actinin, Cx40, Cx43	NYR

Abbreviations: A, atrium; ACh, acetylcholine; AP, action potentia; APD, action potential duration; CV, conduction velocity; Cx, connexin; ECM, extracellular matrix; ERP, effective refractory period; ICa(T)T-type calcium current; IK, delayed rectifier current; MLC-2v, ventricular isoform of myosin regulatory light chain 2; MMP2, matrix metalloproteinase 2; NCX, sodium-calcium exchanger; NYR, not yet reported; SM, smooth muscle; TGFβ1, transforming growth factor-β1; V, ventricle; ±, inconsistent between reports; ↑, increased; ↓, decreased; ↔, unchanged; Ø, presence or gain of.

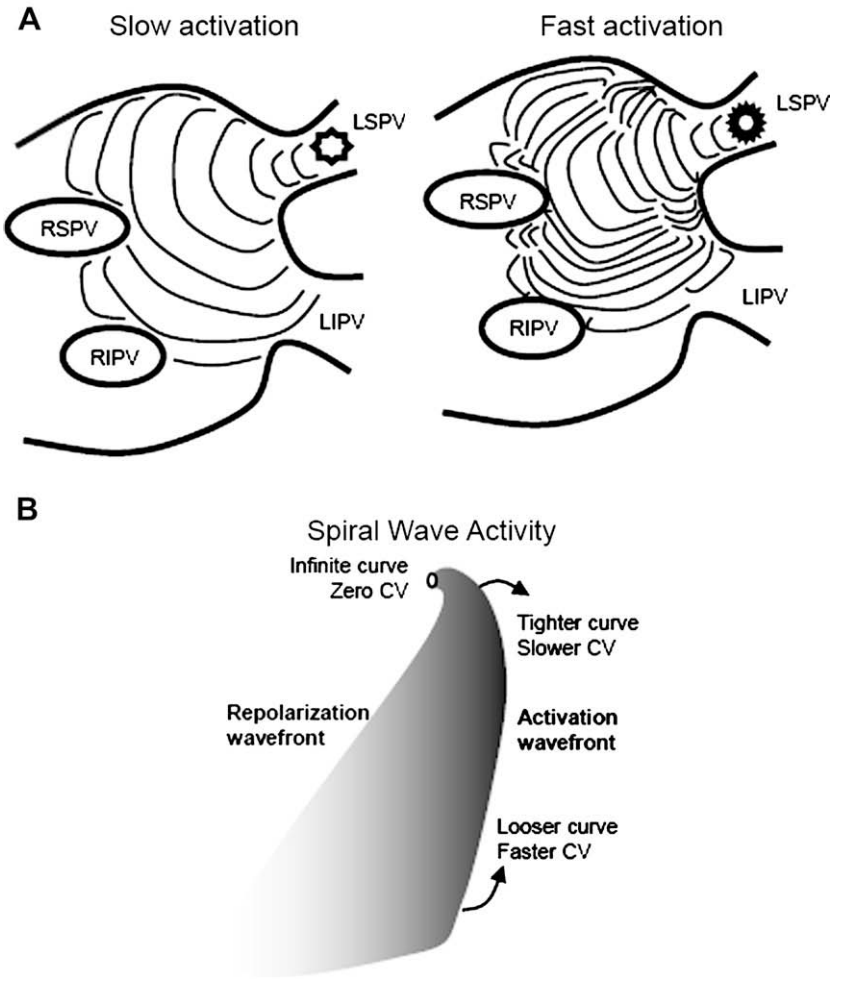

Fig. 1. Schematic of fibrillatory conduction patterns. (*A*) Fibrillatory conduction away from a point source in the left superior pulmonary vein. The schematic depicts normal uniform conduction at slower activation rates, and conduction breakdown as heterogeneities within tissue and curvature around obstacles affects CV at extremely fast activation rates. The breakdown of uniform conduction gives a surface electrocardiographic appearance of disorganization and fibrillation. LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein. (*B*) Spiral wave conduction. The angle of curvature is a determinant of CV, in which slow conduction occurs at the tighter portion of the curve and more rapid conduction occurs at the looser portion of the curve. At the core of the spiral, curvature is infinite; thus, conduction is zero.

theory of reentry, in which the central zone of block is unexcitable during reentry,[5] accounting for the ability of spiral waves to meander throughout the atria or remain spatially fixed. Fibrillation can occur with a single spiral (the so-called ''mother rotor'') if activation is fast enough to cause fibrillatory conduction to occur away from the spiral. More commonly, fibrillation occurs in the presence of multiple spirals that tend to be transient in space and time. Fibrillation is sustained as each spiral progressively spawns other spirals that meander through the tissue.

An important element in sustaining AF is the electrical and structural remodeling caused by AF that promotes AF maintenance and recurrence (AF begets AF).[6,7] This parallels the clinical perception that with time, it becomes more and more difficult to keep patients with AF in sinus rhythm, as expressed by the phrase ''domestication of atrial fibrillation,'' attributed to Mauricio Rosenbaum.[7] Electrophysiologic remodeling includes alteration of ionic current densities, heterogeneous shortening of the effective refractory period (ERP), and decrease of the CV, among others, whereas structural remodeling denotes atrial dilation, interstitial fibrosis, atrial myocyte ultrastructural changes, and altered expression of structural and gap junctional proteins.[8–14] These

findings have not been observed in all animal models. Each one is characterized by a unique set of adaptive changes.

Animal Models of Atrial Fibrillation

Autonomic stimulation

Some of the earliest models of AF manipulated autonomic tone in the cardiac atria of dogs. The simplest model involved applying a drop of carbachol to the atrial appendage, which caused sustained AF lasting for the duration of the carbachol exposure.[15] Clamping the appendage separated the fibrillatory source from the substrate, causing cardioversion of the main atrial body but allowing the affected appendage to continue fibrillating. This maneuver supported the idea that fibrillation comes from a rapidly firing point source with fibrillatory conduction away from the stimulus. Atrial muscarinic receptor activation has also been achieved by continuous bilateral electrical stimulation of the cervical vagosympathetic trunks, acetylcholine infusion, or sympathetic denervation, among others.[16–18] The principal electrophysiologic manifestations of parasympathetic stimulation are dramatic shortening of the atrial action potential duration (APD) and ERP caused by activation of the acetylcholine-activated potassium current (IKACh) channel. Point source activation with carbachol causes localized changes, and central stimulation of the vagus causes global, albeit heterogeneous, changes. The novel antiarrhythmic agent NIP-151 potently blocks IKACh with an atrial-specific ERP-prolonging profile, displaying a low proarrhythmic risk, and may be useful for the treatment of AF.[19]

Adrenergic stimulation with isoproterenol or adrenaline also causes AF.[17] Similar to parasympathetic stimulation, the dominant electrophysiologic alteration is shortening of the APD and ERP. The effect of adrenergic stimulation on the ERP is much more spatially homogeneous, and AF induction is much less common when compared with the prominent and reliable effects of parasympathetic stimulation.[20] Increased slow compound of the delayed rectifier potassium current (IKs) channel activity is the likely source for APD alterations with adrenergic stimulation.

Atrial Burst Pacing

Goats

The first reported method for achieving sustained AF in an animal model was developed in the laboratory of Maurits Allessie.[7] He and his colleagues implanted atrial pacing leads in goats and connected the leads to a computer that initiated AF by burst pacing the atria at a frequency of 64 Hz. In later iterations of the model, the computer was replaced by an implanted pacemaker. The computer or pacemaker monitored atrial rate between bursts, and return of sinus rhythm (defined as slowing of atrial rate lower than a programmed set point) initiated further burst pacing. With this treatment, the episodes of nonsustained AF progressively lengthened over time until sustained AF was achieved several weeks after onset of the burst pacing. The concept that ''AF begets AF'' was first experimentally substantiated in this model. Within 24 hours of burst pacing, the atrial ERP had decreased by 35% without significant change in CV, thus favoring continued fibrillation by shortening the wavelength necessary to sustain reentry. Other electrical changes included a reversion of the physiologic rate adaptation in the ERP and an increase in the rate, inducibility, and stability of AF. Electrical remodeling in this model reversed within 1 week after restoration of sinus rhythm.[21]

Gap junctional remodeling was also observed in the goat AF model.[14] Over a 16-week time course after initiation of burst atrial pacing, connexin 40 (Cx40) expression levels decreased in a heterogeneous fashion (present in some areas of tissue and virtually absent in other areas of the same atrium). Even when Cx40 expression was unaltered, lateralization of connexin expression away from intercalated disks was observed. Expression level and distribution of Cx43 were unaffected. This reduction of Cx40 was found to be completely reversed 4 weeks after return to sinus rhythm.

In addition to the electrical remodeling, structural remodeling was present in the goat. Ausma and colleagues[22] demonstrated that after 9 to 23 weeks, sustained AF led to structural changes in the atrial myocytes similar to those seen in ventricular myocytes from chronic hibernating myocardium. They described myocyte hypertrophy, loss of myofibrils, accumulation of glycogen, changes in mitochondrial shape and size, fragmentation of sarcoplasmic reticulum, and dispersion of nuclear chromatin. No signs of cellular degeneration or changes in the interstitial space were found. The time course of structural remodeling was somewhat variable.[13] Progressive morphologic changes in mitochondria and sarcoplasmic reticulum and homogeneous chromatin distribution peaked 1 week after AF induction, and myolysis and glycogen accumulation were maximal after 8 weeks of AF. Myocyte dedifferentiation has been implicated as an important element in the structural remodeling process. This concept is supported by observation of altered expression patterns of myocyte structural proteins, reexpression of fetal proteins like α-smooth muscle actin, and down-regulation of cardiotin (the A-I junctional part of titin and desmin) at progressive time

points that correlate with the ultrastructural observations of structural remodeling. Unlike other animal models (and perhaps the human condition), there is no significant atrial fibrosis in the burst pacing goat model.[13]

The electrical, structural, and gap junctional remodeling in the goat model affect the response to antiarrhythmic drugs.[6] Duytschaever and colleagues[23] compared class I and class III drugs in the AF-induced electrophysiologically remodeled atria of the goat, finding that the effects of flecainide on atrial conduction were not altered after 48 hours of sustained AF, whereas the effects of the rapid component of the delayed rectifier potassium current (IKr) blockers d-sotalol and ibutilide on ERP were lost over the same time course. These data suggest that the kinetics of sodium current (INa) (or at least the interaction with flecainide) are probably not significantly affected by electrical remodeling, although this remains to be determined. In a later work, Blaauw and colleagues[24] demonstrated that AVE0118 administration (blockade of the ultra rapid component of delayed rectifier potassium current [IKur], the transient outward current [ITo], and IKACh) restored the ERP prolonging effects of dofetilide and ibutilide. These data suggest a possible synergy in function of potassium channels that could be exploited therapeutically.

Dogs

Rapid atrial pacing at a rate of 400 or 600 beats per minute (bpm) in dogs increases AF inducibility.[8,9,25] An important element of this model is that it is not a sustained AF model. The pacing emulates sustained atrial tachycardia (AT), although several investigators have shown that episodes of acutely induced AF are progressively longer as a function of time since the start of rapid atrial pacing. Ventricular rate is generally controlled in the model by AV node ablation and ventricular pacemaker implantation.

Like the goat-sustained AF model, electrophysiologic remodeling is prominent in the dog AT model. Gaspo and colleagues[26] demonstrated that rapid atrial pacing decreased CV and the ERP. The ERP changes were maximal within 7 days of pacing onset, but the CV changes did not peak until 42 days after the start of atrial tachypacing. Fareh and colleagues[9] found an increase in the heterogeneity of ERP across the atria in the same model.

In a later work, Yue and colleagues[8] provided a potential molecular basis for these functional effects. They described changes in atrial gene expression at the RNA level that correlated with altered levels of ionic currents. Rapid atrial pacing decreased expression of KV4.3 (a subunit of Ito1), CaV1.2 [a subunit of ICa(L)], and NaV1.5 (a subunit of INa). They observed no changes in KV7.1 (a subunit of IKs), KV11.1 (a subunit of IKr), Kir2.1 (the inward rectifier current [IK1]), or NCX (the sodium-calcium exchanger). Voigt and colleagues[27] recently showed that AT also increases agonist-independent constitutive IKACh single-channel activity by enhancing spontaneous channel opening.

Shiroshita-Takeshita and colleagues[28] evaluated the role of anti-inflammatory drugs in the dog AT model, showing that prednisone, but not ibuprofen or cyclosporine-A, significantly reduced electrophysiologic remodeling. Prednisone was also associated with a decrease of C-reactive protein (CRP) and endothelial nitric oxide synthase levels, suggesting an anti-inflammatory mechanism of action. Evidence also suggests that heat shock proteins (HSPs) may have some protecting role against AF in the dog model. Brundel and colleagues[29] evaluated the effect of HSP induction in this model, demonstrating that HSP induction protects against AT-induced remodeling and that the orally administered HSP inducer geranylgeranylacetone suppressed AF promotion in remodeled atria.

Investigation of structural remodeling has been limited in the dog atrial tachypacing model. The only investigation specifically looking at atrial histology showed no significant increase in fibrosis after 1 week of atrial tachypacing.[11]

Heart Failure

Dogs

Although electrical remodeling seems to be the main determinant for AF promotion in the AT dog model, structural remodeling seems to play the major role in heart failure (HF) models of AF inducibility.[10] HF is generally induced in dogs by right ventricular pacing at 240 bpm for 2 to 3 weeks, followed by pacing at 220 bpm for 3 weeks, generating a tachycardiomyopathy.[30] Reports of cellular electrophysiologic remodeling caused by HF have been inconsistent. Li and colleagues[11] reported no change in average atrial CV or ERP, although they did see heterogeneity in atrial conduction with discrete areas of slow conduction. Cha and colleagues[31] described a 50% increase in the ERP with ventricular tachypacing, and these researchers did not report CV. These functional changes correlated with ionic current changes, including reduced ICa(L), Ito, and IKs, and increased NCX and IK1. These alterations of ionic current densities completely reverse after 4 weeks of recovery.[31]

Structural remodeling, conversely, is currently believed to be the main determinant of induction and maintenance of AF in this model.[10,11,31]

Experimental HF causes hypertrophy of atrial myocytes and extensive interstitial fibrosis. Molecular analyses of atrial tissues reveal upregulation of several extracellular matrix mRNAs after 2 weeks of ventricular tachypacing, including eight collagen genes, fibrillin-1, and matrix metalloproteinase 2 (MMP2).[32] Five weeks after ventricular tachypacing is discontinued, echocardiographic measures of atrial and ventricular structure and function normalize and the duration of induced episodes of AF is decreased. In spite of reversing the HF phenotype, atrial interstitial fibrosis, conduction abnormalities, and AF inducibility are not reversible, at least in the short term.[33]

The effects of combined atrial and ventricular burst pacing in dogs seem to be the average of individual atrial or ventricular burst pacing effects on electrical and structural remodeling. A comparison of dogs exposed to the combined effects of 1 week of atrial tachypacing and 2 weeks of ventricular tachypacing showed increased AF inducibility and increased duration of nonsustained AF episodes after induction.[34] The atrial ERP did not change in this group (in contrast to a 50% increase in the ERP with ventricular tachypacing alone or a 30% decrease in the ERP with atrial tachypacing alone). Ionic current changes in the combined atrial and ventricular tachypacing group also seemed to be the average of effects seen with atrial or ventricular tachypacing alone: Ito decreased 50% with all three models; IKs decreased to same level with ventricular tachypacing and combined tachypacing but did not change with atrial tachypacing; IK1 increased 70% with atrial tachypacing and 37% with combined tachypacing but did not change with ventricular tachypacing; and ICa(L) decreased 31% with ventricular tachypacing, 50% with combined tachypacing, and 60% with atrial tachypacing. The structural effects in the dog model of combined tachypacing have not yet been reported.

Pigs

We reported phenotyping data in the pig model of burst atrial pacing using the Allessie protocol of 64-Hz atrial bursting until sustained AF develops.[7] Unlike the goat model, in which the ventricular rate is not overly fast, the ventricular response rate averages 270 bpm in the pig model. This sustained high rate gives a combined atrial tachyarrhythmia and ventricular HF model. In this model, we found atrial structural remodeling that seemed to be the combined effects reported in the goat AF and dog HF models: the pigs had four-chamber cardiac dilation and dysfunction, cellular hypertrophy, myolysis, inflammation, and fibrosis.[35]

In a similar model, in which the right atrial appendages of pigs were pacing at 600 bpm for 3 to 6 weeks, Lin and colleagues[36] described an increase in the atrial extracellular matrix, correlating with fibronectin-1, fibrillin-1, and fibromodulin gene upregulation. Lai and colleagues[37] demonstrated increases in the ventricular isoform of myosin regulatory light chain 2 (MLC-2v) in atrial tissue in the same pig atrial tachypacing model. The electrophysiologic alterations of the pig model have not yet been evaluated.

Sterile Pericarditis

The dog model of sterile pericarditis was developed in the lab of Al Waldo. These researchers created pericarditis by irritating the pericardium with talcum after sterile mediastinotomy and pericardiotomy. The predominant arrhythmia in the model is atrial flutter, but AF is also induced.[38] Kumagai and colleagues[39] showed that unstable and migratory reentrant circuits of extremely short cycle length, principally involving the atrial septum, seem to be responsible for arrhythmia maintenance. Bachmann's bundle seemed critical to maintenance of the arrhythmia because its ablation terminated or prevented inducibility.[40] Heterogeneous reductions in CV have also been described in the model. The conduction changes correlated with a measurable transmural gradient in Cx40 and Cx43 expression.[41] Connexins were absent in the epicardium, decreased in the midmyocardium, and completely normal in the endocardium, likely attributable to an epicardially centered inflammatory response. Administration of atorvastatin 1 week before the pericardiotomy lowered the CRP level, increased the ERP, abbreviated intra-atrial conduction time, and shortened AF duration in this model, likely through its anti-inflammatory properties.[42] In a recent work, prednisone also attenuated tissue inflammation and decreased CRP levels, which returned to baseline after 4 days, correlating with a virtual absence of sustained arrhythmia.[43]

Aging

Increased age is a well-known risk factor for AF.[3] Anyukhovsky and colleagues[44] compared various parameters in older dogs (>8 years old) with those in younger adult dogs (1–5 years old). They found significant morphologic differences of the action potential (AP), including a decrease in peak and plateau AP voltage, a decrease in the rate of cellular depolarization, a slight decrease in resting membrane potential (−70 in older dogs versus −75 in younger dogs), and an increased dispersion of APD across the tissue. The P wave duration was

also increased in the older dogs. The CV of regularly timed beats was similar in adult and old dogs, but it decreased for premature beats in older dogs. These investigators also found significant fibrosis in the older animals. From these data, they speculated that the fibrosis, slowed conduction of premature beats, and increased heterogeneity of repolarization may be important determinants of the initiation and subsequent stabilization of AF in the elderly.[45]

Transgenic mice

Atrial electrophysiologic effects and AF have been reported in several transgenic mouse lines. The possibility that inflammation and fibrosis affect AF vulnerability was shown by transgenic mice overexpressing tumor necrosis factor-α,[46] transforming growth factor-β,[47] Rac1 guanosine triphosphatase (GTPase)[48] and angiotensin-converting enzyme.[49] Each of these proteins affects inflammation or fibrosis of the atria, and each mouse had an increased propensity to AF. The connection between repolarization and fibrillatory potential was confirmed by mice overexpressing Kir 2.1 (IK1)[50] and KCNQ1 (IKs).[51] Overexpression of Kir 2.1 accelerated and stabilized fibrillatory rotors (ventricular in this case; however, conceptually, the same principle holds in the atria). The KCNQ1-overexpressing mice had AF with adrenergic stimulation–mediated amplification of the IKs effects on repolarization. Several other transgenic lines have shown AF in conjunction with cardiomyopathies or structural heart disease, which confounds the connection between the transgene and AF. Although the direct applicability of mouse AF to the human condition is unclear, these models can be taken as interrogations about the functional effects of particular proteins or systems on fibrillatory potential.

SUMMARY

At first glance, with this wide array of pathophysiologic findings in varying animal models, it is difficult to see any commonalities. That may be the most important point of this review. Human AF is likely an end point of numerous disease states, structural alterations, or inherited defects. We need to keep this in mind when interpreting the animal data. The goat burst atrial pacing model has no underlying structural disease or atrial pathologic changes caused by repetitive burst stimulation from an atrial point source, similar to the reported situation of paroxysmal AFn emanating from the PVs. The dog tachypacing cardiomyopathy without primary atrial disease is potentially analogous to AF in patients who have idiopathic ventricular myopathies (with the caveat that any primary atrial or noncardiac manifestations of the underlying disease process would not be a part of the tachypacing model). The poor rate control of the pig model could compare with the situation of primary AF with cardiomyopathy from similarly poor rate control. Although each of these situations has AF as a component, each is unique, and the corresponding animal model must likewise be individualized.

Common themes that emerge from this survey of animal models include the frequent implications across models that intra-atrial heterogeneity (of conduction, repolarization, or cellular architecture), alterations in repolarization (shortened or prolonged but almost always abnormal), and CV slowing (homogeneous or heterogeneous) play a role in the pathogenesis of AF. The frequency of these observations suggests that these findings may be common to the fibrillation process, and therefore that therapeutic alterations targeting these areas may bear fruit. Ultimately, any conclusions drawn from animal models, and any suggested therapies, must be tested for validity in humans. Still, the similarities between the various human diseases and their corresponding animal models provide an excellent starting point for these investigations.

REFERENCES

1. Nattel S. Therapeutic implications of atrial fibrillation mechanisms: can mechanistic insights be used to improve AF management? Cardiovasc Res 2002; 54:347–60.
2. Chen PS, Tan AY. Autonomic nerve activity and atrial fibrillation. Heart Rhythm 2007;4:S61–4.
3. Allessie MA, Boyden PA, Camm AJ, et al. Pathophysiology and prevention of atrial fibrillation. Circulation 2001;103:769–77.
4. Jaïs P, Haïssaguerre M, Shah DC, et al. A focal source of atrial fibrillation treated by discrete radiofrequency ablation. Circulation 1997;95:572–6.
5. Allessie MA, Bonke FI, Schopman FJ. Circus movement in rabbit atrial muscle as a mechanism of tachycardia. III. The "leading circle" concept: a new model of circus movement in cardiac tissue without the involvement of an anatomical obstacle. Circ Res 1977;41:9–18.
6. Chou CC, Chen PS. New concepts in atrial fibrillation: mechanism and remodeling. Med Clin North Am 2008;92:53–63, x.
7. Wijffels MC, Kirchhof CJ, Dorland R, et al. Atrial fibrillation begets atrial fibrillation—a study in awake chronically instrumented goats. Circulation 1995; 92:195468.

8. Yue LX, Melnyk P, Gaspo R, et al. Molecular mechanisms underlying ionic remodeling in a dog model of atrial fibrillation. Circ Res 1999;84:776–84.
9. Fareh S, Villemaire C, Nattel S. Importance of refractoriness heterogeneity in the enhanced vulnerability to atrial fibrillation induction caused by tachycardia-induced atrial electrical remodeling. Circulation 1998;98:2202–9.
10. Shi Y, Ducharme A, Li D, et al. Remodeling of atrial dimensions and emptying function in canine models of atrial fibrillation. Cardiovasc Res 2001; 52:217–25.
11. Li DS, Fareh S, Leung TK, et al. Promotion of atrial fibrillation by heart failure in dogs—atrial remodeling of a different sort. Circulation 1999;100:87–95.
12. Dispersyn GD, Ausma J, Thoné F, et al. Cardiomyocyte remodelling during myocardial hibernation and atrial fibrillation: prelude to apoptosis. Cardiovasc Radiol 1999;43:947–57.
13. Ausma J, Litjens N, Lenders MH, et al. Time course of atrial fibrillation-induced cellular structural remodeling in atria of the goat. J Mol Cell Cardiol 2001;33: 2083–94.
14. van der Velden HM, Ausma J, Rook MB, et al. Gap junctional remodeling in relation to stabilization of atrial fibrillation in the goat. Cardiovasc Res 2000; 46:476–86.
15. Rothberger C, Winterberg H. Ueber Vorhofflimmern und Vorhofflattern. Archiv Ges Physiol 1914;160: 42–90.
16. Goldberger AL, Pavelec RS. Vagally-mediated atrial fibrillation in dogs: conversion with bretylium tosylate. Int J Cardiol 1986;13:47–55.
17. Sharifov OF, Fedorov VV, Beloshapko GG, et al. Roles of adrenergic and cholinergic stimulation in spontaneous atrial fibrillation in dogs. J Am Coll Cardiol 2004;43:483–90.
18. Olgin JE, Sih HJ, Hanish S, et al. Heterogeneous atrial denervation creates substrate for sustained atrial fibrillation. Circulation 1998;98:2608–14.
19. Hashimoto N, Yamashita T, Tsuruzoe N. Characterization of in vivo and in vitro electrophysiological and antiarrhythmic effects of a novel IKACh blocker, NIP-151: a comparison with an IKr-blocker dofetilide. J Cardiovasc Pharmacol 2008;51:162–9.
20. Liu L, Nattel S. Differing sympathetic and vagal effects on atrial fibrillation in dog: role of refractoriness heterogeneity. Am J Phys 1997;273:H805–16.
21. Ausma J, van der Velden HM, Lenders MH, et al. Reverse structural and gap-junctional remodeling after prolonged atrial fibrillation in the goat. Circulation 2003;107:2051–8.
22. Ausma J, Wijffels M, Thoné F, et al. Structural changes of atrial myocardium due to sustained atrial fibrillation in the goat. Circulation 1997;96:3157–63.
23. Duytschaever M, Blaauw Y, Allessie M. Consequences of atrial electrical remodeling for the anti-arrhythmic action of class IC and class III drugs. Cardiovasc Res 2005;67:69–76.
24. Blaauw Y, Schotten U, van Hunnik A, et al. Cardioversion of persistent atrial fibrillation by a combination of atrial specific and non-specific class III drugs in the goat. Cardiovasc Res 2007;75:89–98.
25. Verheule S, Wilson E, Banthia S, et al. Direction-dependent conduction abnormalities in a canine model of atrial fibrillation due to chronic atrial dilatation. Am J Physiol Heart Circ Physiol 2004;287: H634–44.
26. Gaspo R, Bosch RF, Talajic M, et al. Functional mechanisms underlying tachycardia-induced sustained atrial fibrillation in a chronic dog model. Circulation 1997;96:4027–35.
27. Voigt N, Maguy A, Yeh YH, et al. Changes in I K, ACh single-channel activity with atrial tachycardia remodelling in canine atrial cardiomyocytes. Cardiovasc Res 2008;77:35–43.
28. Shiroshita-Takeshita A, Brundel BJ, Lavoie J, et al. Prednisone prevents atrial fibrillation promotion by atrial tachycardia remodeling in dogs. Cardiovasc Res 2006;69:865–75.
29. Brundel BJ, Shiroshita-Takeshita A, Qi X, et al. Induction of heat shock response protects the heart against atrial fibrillation. Circ Res 2006;99: 1394–402.
30. Li D, Melnyk P, Feng J, et al. Effects of experimental heart failure on atrial cellular and ionic electrophysiology. Circulation 2000;101:2631–8.
31. Cha TJ, Ehrlich JR, Zhang L, et al. Dissociation between ionic remodeling and ability to sustain atrial fibrillation during recovery from experimental congestive heart failure. Circulation 2004;109: 412–8.
32. Cardin S, Libby E, Pelletier P, et al. Contrasting gene expression profiles in two canine models of atrial fibrillation. Circ Res 2007;100:425–33.
33. Shinagawa K, Shi YF, Tardif JC, et al. Dynamic nature of atrial fibrillation substrate during development and reversal of heart failure in dogs. Circulation 2002;105:2672–8.
34. Cha TJ, Ehrlich JR, Zhang L, et al. Atrial ionic remodeling induced by atrial tachycardia in the presence of congestive heart failure. Circulation 2004;110: 1520–6.
35. Bauer A, McDonald AD, Donahue JK. Pathophysiological findings in a model of persistent atrial fibrillation and severe congestive heart failure. Cardiovasc Res 2004;61:764–70.
36. Lin CS, Lai LP, Lin JL, et al. Increased expression of extracellular matrix proteins in rapid atrial pacing-induced atrial fibrillation. Heart Rhythm 2007;4: 938–49.
37. Lai LP, Lin JL, Lin CS, et al. Functional genomic study on atrial fibrillation using cDNA microarray and two-dimensional protein electrophoresis

techniques and identification of the myosin regulatory light chain isoform reprogramming in atrial fibrillation. J Cardiovasc Electrophysiol 2004;15: 214–23.
38. Page PL, Plumb VJ, Okumura K, et al. A new model of atrial flutter. J Am Coll Cardiol 1986;8:872–9.
39. Kumagai K, Khrestian C, Waldo AL. Simultaneous multisite mapping studies during induced atrial fibrillation in the sterile pericarditis model—insights into the mechanism of its maintenance. Circulation 1997;95:511–21.
40. Kumagai K, Uno K, Khrestian C, et al. Single site radiofrequency catheter ablation of atrial fibrillation: studies guided by simultaneous multisite mapping in the canine sterile pericarditis model. J Am Coll Cardiol 2000;36:917–23.
41. Ryu K, Li L, Khrestian CM, et al. Effects of sterile pericarditis on connexins 40 and 43 in the atria: correlation with abnormal conduction and atrial arrhythmias. Am J Physiol Heart Circ Physiol 2007;293: H1231–41.
42. Kumagai K, Nakashima H, Saku K. The HMG-CoA reductase inhibitor atorvastatin prevents atrial fibrillation by inhibiting inflammation in a canine sterile pericarditis model. Cardiovasc Res 2004;62:105–11.
43. Goldstein RN, Ryu K, Khrestian C, et al. Prednisone prevents inducible atrial flutter in the canine sterile pericarditis model. J Cardiovasc Electrophysiol 2008;19:74–81.
44. Anyukhovsky EP, Sosunov EA, Plotnikov A, et al. Cellular electrophysiologic properties of old canine atria provide a substrate for arrhythmogenesis. Cardiovasc Res 2002;54:462–9.
45. Anyukhovsky EP, Sosunov EA, Chandra P, et al. Age-associated changes in electrophysiologic remodeling: a potential contributor to initiation of atrial fibrillation. Cardiovasc Res 2005;66:353–63.
46. Saba S, Janczewski AM, Baker LC, et al. Atrial contractile dysfunction, fibrosis, and arrhythmias in a mouse model of cardiomyopathy secondary to cardiac-specific overexpression of tumor necrosis factor-α. Am J Physiol Heart Circ Physiol 2005;289: H1456–67.
47. Verheule S, Sato T, Everett T 4th, et al. Increased vulnerability to atrial fibrillation in transgenic mice with selective atrial fibrosis caused by overexpression of TGF-beta1. Circ Res 2004;94:1458–65.
48. Adam O, Frost G, Custodis F, et al. Role of Rac1 GTPase activation in atrial fibrillation. J Am Coll Cardiol 2007;50:359–67.
49. Xiao HD, Fuchs S, Campbell DJ, et al. Mice with cardiac-restricted angiotensin-converting enzyme (ACE) have atrial enlargement, cardiac arrhythmia, and sudden death. Am J Pathol 2004;165:1019–32.
50. Noujaim SF, Pandit SV, Berenfeld O, et al. Up-regulation of the inward rectifier K+ current (I K1) in the mouse heart accelerates and stabilizes rotors. J Physiol 2007;578:315–26.
51. Sampson KJ, Terrenoire C, Cervantes DO, et al. Adrenergic regulation of a key cardiac potassium channel can contribute to atrial fibrillation: evidence from an I Ks transgenic mouse. J Physiol 2008;586:627–37.