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Information Learned from Animal Models of Atrial Fibrillation

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Synopsis

Animal models of atrial fibrillation have taught us about mechanisms of this common disease. A variety of animal models exist, including models of lone atrial fibrillation and models of atrial fibrillation in the setting of heart failure, aging or pericardial inflammation. This chapter reviews these various models.

Keywords

cardiac arrhythmia; atrial fibrillation; animal model; remodeling

Introduction

Atrial Fibrillation (AF) continues to be the most common arrhythmia encountered clinically and is responsible for significant morbidity and healthcare cost. Therapy for AF has advanced significantly in recent years, mainly due to 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 either resists cardioversion or reverts quickly in spite of cardioversion. AF requires a trigger for its initiation and a suitable electrophysiological and/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 either 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

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stimulus site is activating at a rate that cannot be sustained through the mass of tissue, so conduction breaks down distal to the initiating site (Figure 1A). Thus, 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 anatomical separation between the two pathways, spiral wave reentry is dependent on functional properties of the tissue. Excitation occurs in a vortex spinning around an excitable, but unexcited core. Conduction velocity is determined by the curvature of the spiral, so conduction velocity is fastest at the periphery of the wave where curvature is widest. Conduction velocity slows as the curvature increases closer to the core, and conduction is non-existent at the core of the spiral where curvature is essentially infinite (Figure 1B). This contrasts the so called “leading circle” theory of reentry where the central zone of block is unexcitable during reentry(5), accounting for the ability of spiral waves to either 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 both 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, expressed by the phrase “domestication of atrial fibrillation”, attributed to Mauricio Rosenbaum (7). Electrophysiological remodeling includes alteration of ionic current densities, heterogeneous shortening of the effective refractory period (ERP) and decrease of the conduction velocity (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 AF

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 principle electrophysiological manifestations of parasympathetic stimulation are dramatic shortening of atrial action potential duration (APD) and ERP caused by activation of the IK_{ACh} 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 potentially blocks IK_{ACh} 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 electrophysiological alteration is shortening of

APD and ERP. The effect of adrenergic stimulation on ERP is much more spatially homogenous and AF induction is much less common when compared to the prominent and reliable effects of parasympathetic stimulation(20). Increased 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). They implanted atrial pacing leads in goats and connected the leads to a computer that initiated AF by burst pacing the atria at 64 Hz frequency. 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 below a programmed set-point) initiated further burst pacing. With this treatment, the episodes of non-sustained 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, atrial ERP decreased by 35% without significant change in conduction velocity, thus favoring continued fibrillation by shortening the wavelength necessary to sustain reentry. Other electrical changes included a reversion of the physiological rate adaptation in ERP and an increase in rate, inducibility and stability of AF. Electrical remodeling in this model reversed within one 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 expression levels decreased in a heterogeneous fashion (present in some areas of tissue and virtually absent in other areas of the same atrium). Even where connexin 40 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 also present in the goat. Ausma et al. 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 (22). No signs of cellular degeneration or changes in the interstitial space were found. The time course of structural remodeling was somewhat variable (13): Progressive morphological changes in mitochondria and sarcoplasmic reticulum and homogeneous chromatin distribution peaked 1 week after AF induction; 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, re-expression of fetal proteins like α -smooth muscle actin, and downregulation of cardiotin, 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 et al. 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 IKr

blockers d-sotalol and ibutilide on ERP were lost over the same time course (23). These data suggest that kinetics of INa (or at least the interaction with flecainide) is probably not significantly affected by electrical remodeling, though this remains to be determined. In a later work, Blaauw et al. demonstrated that AVE0118 administration (blockade of IK_{Kr}, I_{to} and IK_{ACh}) 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 (24).

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, electrophysiological remodeling is prominent in the dog AT model. Gaspo et al. demonstrated that rapid atrial pacing decreased CV and ERP (26). 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 et al. found an increase in heterogeneity of ERP across the atria in the same model(9).

In a later work, Yue et al. provided a potential molecular basis for these functional effects (8). 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 I_{to1}), 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 (IK1) or NCX (the sodium-calcium exchanger). Voigt et al. recently showed that AT also increases agonist-independent, constitutive IK_{ACh} single-channel activity by enhancing spontaneous channel opening (27).

Shiroshita-Takeshita et al. evaluated the role of anti-inflammatory drugs in the dog AT model, showing that prednisone, and not ibuprofen or cyclosporine-A, significantly reduced electrophysiological remodeling (28). Prednisone was also associated with a decrease of C-reactive protein 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 et al. evaluated the effect of HSP induction in this model (29), 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

While electrical remodeling appears 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 2-3 weeks, followed by 220 bpm for 3 weeks, generating a tachycardiomyopathy (30). Reports of cellular electrophysiological remodeling caused by HF have been inconsistent. Li

et al. reported no change in average atrial conduction velocity or ERP, although they did see heterogeneity in atrial conduction with discrete areas of slow conduction (11). Cha et al. described a 50% increase in ERP with ventricular tachypacing, and they did not report conduction velocity (31). These functional changes correlated with ionic current changes including reduced $ICa(L)$, I_{to} and I_K s and increased NCX and $IK1$. These alterations of ionic current densities completely reverse after 4 weeks of recovery (31).

Structural remodeling, on the other hand, 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 8 collagen genes, fibrillin-1, and 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 appear 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 atrial and 2 week ventricular tachypacing showed increased AF inducibility and increased duration of non-sustained AF episodes after induction (34). The atrial ERP did not change in this group (in contrast to a 50% increase in ERP with ventricular tachypacing alone or a 30% decrease in 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 either atrial or ventricular tachypacing alone: I_{to} decreased 50% with all 3 models; I_K s 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; $ICa(L)$ 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 Allesie protocol of 64 Hz atrial bursting until sustained atrial fibrillation develops (7). Unlike the goat model, where the ventricular rate is not overly fast, in the pigs the ventricular response rate averages 270 bpm. This sustained high rate gives a combined atrial tachyarrhythmia and ventricular heart failure 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 a four chamber cardiac dilation and dysfunction, cellular hypertrophy, myolysis, inflammation and fibrosis (35).

In a similar model, where the right atrial appendages of pigs were pacing at 600 bpm for 3-6 weeks, Lin et al. described an increase in the atrial extracellular matrix, correlating with fibronectin-1, fibrillin-1 and fibromodulin gene upregulation(36). Lai et al. demonstrated increases in the ventricular isoform of myosin regulatory light chain 2 (MLC-2v) in atrial tissue in the same pig atrial tachypacing model(37). 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. They created pericarditis by irritating the pericardium with talcum after sterile mediastinotomy and

pericardiectomy. The predominant arrhythmia in the model is atrial flutter but AF is also induced (38). Kumagai et al. showed that unstable and migratory reentrant circuits of very short cycle length, principally involving the atrial septum, appear to be responsible for arrhythmia maintenance (39). Bachmann's bundle appeared critical to maintenance of the arrhythmia, since its ablation terminated or prevented inducibility (40). Heterogeneous reductions in conduction velocity 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 mid-myocardium, and completely normal in the endocardium, likely due to an epicardially centered inflammatory response. Administration of atorvastatin one week before the pericardiectomy lowered the CRP level, increased the ERP, abbreviated intra-atrial conduction time and shortened AF duration in this model, likely through its antiinflammatory properties (42). In a recent work, prednisone also attenuated tissue inflammation and decreased CRP levels, which returned to baseline after four days, correlating with a virtual absence of sustained arrhythmia (43).

Aging

Increased age is a well known risk factor for AF (3). Anyukhovsky et al. compared various parameters in older dogs (>8 years old) to younger adult dogs (1-5 years old). They found significant morphological differences of the 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 vs. -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. They also found significant fibrosis in the older animals (44). From these data, the authors speculated that the fibrosis, slowed conduction of premature beats, and increased heterogeneity of repolarization may be an important determinant of both the initiation and subsequent stabilization of AF in the elderly (45).

Transgenic Mice

Atrial electrophysiological 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 GTPase (48) and angiotensin converting enzyme (49). Each of these proteins affects inflammation and/or fibrosis of the atria, and each mouse had 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, but 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 atrial fibrillation in conjunction with cardiomyopathies or structural heart disease, which confounds the connection between the transgene and AF. While 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.

Conclusions

Translation of animal results into an understanding of human disease

At first glance, with this wide array of pathophysiological findings in varying animal models, it is difficult to see any commonalities. That may be the most important point of this review. Human atrial fibrillation is likely an endpoint of numerous disease states, structural alterations

or inherited defects. We need to keep these in mind when interpreting the animal data. The goat burst atrial pacing model has no underlying structural disease and atrial pathology caused by repetitive burst stimulation from an atrial point source, similar to the reported situation of paroxysmal atrial fibrillation emanating from the pulmonary veins. The dog tachypacing cardiomyopathy without primary atrial disease is potentially analogous to AF in patients with idiopathic ventricular myopathies (with the caveat that any primary atrial or non-cardiac 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 to the situation of primary AF with cardiomyopathy from similarly poor rate control. While 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 (either shortened or prolonged but almost always abnormal), and conduction velocity slowing (homogeneous or heterogeneous) play a role in 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.

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Figure 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 break down as heterogeneities within tissue and curvature around obstacles affect conduction velocity at very fast activation rates. The breakdown of uniform conduction gives a surface ECG appearance of disorganization and fibrillation. Abbreviations: LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein. B. Spiral wave conduction. The angle of curvature is a determinant of conduction velocity, where 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 so conduction is zero.

Table 1

Clinical Paradigms in Animal Models of Atrial Fibrillation										
Model	Autonomic Stimulation		AT		HF		AT + HF		Sterile Pericarditis	Aging
Species	Dogs		Dogs		Dogs		Dogs		Dogs	Dogs
Atrial Fibrillation	Sustained		↑ inducibility		↑ inducibility		Sustained		↑ inducibility	↑ inducibility
Electrophysiological 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, ICaL (adrenergic)	NYR	↓ Ito, ICaL, INa Ø IKs, IKr, NCX ↑ IK1, IKAch	↓ Ito, ICaL, IKs Ø ICaT, IKr, IK1, IKur ↑ NCX	↓ ICaL, ±↓ Ito, IKs Ø NCX ↑ IK1	NYR	NYR	NYR		
mRNA Expression	NYR	NYR	↓ KCND3, CACNA1C, SCN5A ↔ KCNQ1, KCNH2, KCNJ2,3,5, SLCBA1	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										
Anatomical	Normal	↑ atrial size + hypertrophy, myolysis, glycogen accumulation Ø fibrosis or apoptosis	↑ atrial size Ø fibrosis or hypertrophy	↑ A & V size + fibrosis, hypertrophy	↑ A & V size	↑ A & V size + fibrosis, apoptosis, inflammation, hypertrophy, myolysis	Epicardial: apoptosis, inflammation, necrosis	+ fibrosis		
mRNA Expression	NYR	NYR	↔ ECM	↑ Collagen, Fibrillin-1, MMP2, TGFβ1, αSM 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, MLC2V Fibromodulin, Collagen	Epicardial: ↑ vimentin ↓ α-actin, Cx40, Cx43	NYR		

Abbreviations--NYR: not yet reported, ±: inconsistent between reports, ↑: increased, ↓: decreased, ↔ unchanged, Ø: absence or loss of, +: presence or gain of