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Review

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Therapeutic advances in atrial fibrillation based on animal models

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Abstract: Atrial fibrillation (AF) is the most prevalent sustained cardiac arrhythmia among humans, with its incidence increasing significantly with age. Despite the high frequency of AF in clinical practice, its etiology and management remain elusive. To develop effective treatment strategies, it is imperative to comprehend the underlying mechanisms of AF; therefore, the establishment of animal models of AF is vital to explore its pathogenesis. While spontaneous AF is rare in most animal species, several large animal models, particularly those of pigs, dogs, and horses, have proven as invaluable in recent years in advancing our knowledge of AF pathogenesis and developing novel therapeutic options. This review aims to provide a comprehensive discussion of various animal models of AF, with an emphasis on the unique features of each model and its utility in AF research and treatment. The data summarized in this review provide valuable insights into the mechanisms of AF and can be used to evaluate the efficacy and safety of novel therapeutic interventions.

Key words: Atrial fibrillation; Animal model; Therapeutic

1 Introduction

Atrial fibrillation (AF) is a frequently encountered clinical condition characterized by rapid atrial arrhythmia, with a prevalence rising considerably with age (Sagris et al., 2022). Apart from advanced age, the American Heart Association has suggested that high-risk factors, such as hypertension, underlying heart disease, and alcohol abuse, can trigger structural and histopathological alterations in the atria, consisting of fibrosis, inflammation, as well as cellular and molecular changes (Siasos et al., 2020). Although AF may develop alone in people without organic heart disease, heart failure, myocardial infarction, and pericarditis all increase the risk of AF.

Since its first identification on the electrocardiogram, AF has been a subject of investigation for a century. The mechanisms of AF can be broadly categorized into electrophysiological and pathophysiological types. The electrophysiological mechanisms encompass both triggering and maintenance mechanisms, with several hypotheses proposed for the latter, including the autoregulatory focal and multiple subwave foldback mechanisms (Wijesurendra and Casadei, 2019). The autoregulatory focal mechanism entails that abnormal autoregulatory discharge points in the atria create focal points of origin for AF, while in the multiple subwave foldback mechanism, a single stable and fast periodic excitation source is unable to maintain consistent conduction, resulting in wave breaks and independent wavelets. The two mechanisms can coexist and are more pronounced in persistent AF (Jalife et al., 1998). The pathophysiological mechanisms are primarily classified into electrical remodeling, structural remodeling, autonomic remodeling, and calcium regulation disorders, resulting from changes in atrial structure (Sy et al., 2023). Electrical remodeling involves changes in the electrophysiological characteristics, such as the shortening of effective atrial expiration and action potential time frames, slowing of action potential conduction velocity, and increased

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dispersion of the expiration period. Structural remodeling is mainly manifested by changes in the ultrastructure of atrial myocytes (Beyer et al., 2021). The autonomic nervous system regulates the electrophysiological characteristics of atrial muscle, and calcium ion affects the conduction and contraction of the heart. The therapeutic strategies for AF include ganglionated plexus (GP) ablation, epicardial botulinum toxin injection, vagus nerve stimulation, renal denervation, stellate ganglion block, baroreceptor activation therapy, and spinal cord stimulation (Linz et al., 2014; Hanna et al., 2021). One of the cardiac autonomic nervous system receptors, G protein-coupled receptor (GPCR) signaling, is also inextricably linked to AF (Lymperopoulos et al., 2021; Carbone et al., 2022). In addition, genetic predisposition and inflammatory factors have been suggested to increase the likelihood of AF. Genome-wide association studies have identified nearly 140 AF loci and pathogenic mutations that cause AF, such as potassium-voltage-gated channel subfamily Q member 1 (KCNQ1), natriuretic peptide A (NPPA), T-box transcription factor 5 (TBX5), and myosin light chain 4 (MYL4) (Roselli et al., 2020; Andersen et al., 2021). However, our understanding of AF mechanisms is still incomplete, and the treatment efficacy is currently limited. The development of animal models has contributed to elucidating the mechanisms of AF, and the effects of certain AF-prone factors such as hypertension and obesity have been investigated on the substrate of AF (Manninger et al., 2018; McCauley et al., 2020).

AF is a prevalent human disorder. In contrast, spontaneous AF is uncommon in small-sized animals, while large animals are prone to its occurrence. Besides, in the majority of experimental models, induced AF typically lasts for less than a day. The principal challenge in establishing AF in animal models stems from the fact that AF in humans is heterogeneous, multifactorial, and slow-developing. Therefore, animal models can imitate limited aspects of human AF and they fail to fully reflect its complex pathophysiology. Given the intricacy of AF, this review aims to summarize the various animal models of AF developed to date and the related advancements in AF treatment. The causative factors of human AF and the respective animal models are listed in Fig. 1.

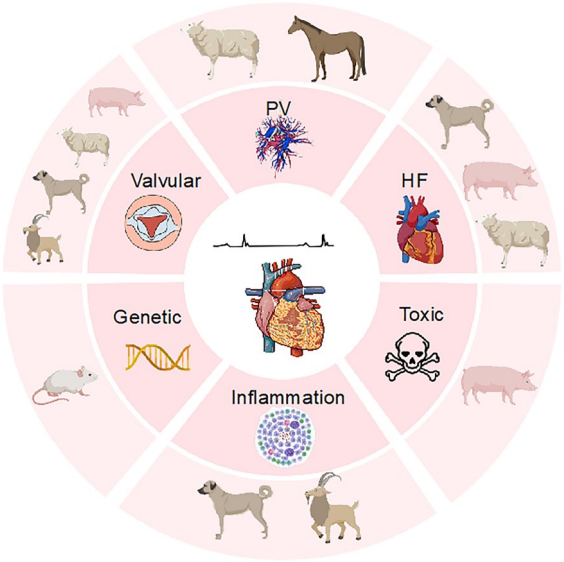

Fig. 1 Causative factors of human atrial fibrillation and the respective animal models. PV: portal vein; HF: heart failure.

2 Small animal models of AF

Rodents and rabbits are typical small animals used in AF animal models (Dobrev and Wehrens, 2018; Clauss et al., 2019). Sprague-Dawley rats in good health have been lately reported to experience spontaneous ventricular arrhythmias (Pereira et al., 2019). In rodents, there has been no record of suddenly developing AF (including rabbits).

2.1 Mice and rats

In the absence of significant physiological perturbations, mice do not often develop AF; nonetheless, genetically induced spontaneous AF can cause severe heart dysfunction, atrial remodeling, and reduced longevity in mice. In terms of atrial morphology and cellular electrophysiology, large animal arrhythmia models are more comparable to human AF; nonetheless, their availability, cost, and reliance on pharmacological probes with poor mechanism specificity are important disadvantages. On the other hand, mouse models have a number of benefits, including a low-cost phenotypic platform and the simplicity of genetic manipulation to reflect clinical variance (Dobrev and Wehrens, 2018).

At present, only a few (transgenic) mouse lines show spontaneous AF. The first account of AF in mice

was published in 1988 (Field, 1988). Under the direction of an atrial-specific atrial natriuretic factor promoter, transgenic mouse lines carrying the oncogene (SV40 big T antigen) were created. In comparison to controls, this method caused the right atrium to expand proliferatively and became 10–20 times larger. Electrocardiographic recordings made in these animals revealed that the advancement of atrial hyperplasia was accompanied by the emergence of supraventricular arrhythmias, including AF (Field, 1988). A mouse strain sensitive to supraventricular arrhythmias was produced by the targeted ablation of connexin40 (Cx40), a connexin that is selectively expressed in atrial myocytes and the ventricular conduction system (Kirchhoff et al., 1998). Atrial arrhythmias, including atrial ectopy, atrial flutter, and AF, were spontaneous and produced in Cx40-deficient ($Cx40^{-/-}$) mice (Santa Cruz et al., 2015). A novel mouse model of atrial cardiomyopathy with spontaneous AF and without molecular or phenotypic changes in the ventricles was created by adeno-associated virus 9 (AAV9)-mediated limited knockdown of liver kinase-B1 (LKB1) in atrial myocytes. Since LKB1 expression is low in paroxysmal-AF (pAF) patients, this model seems to have clinical applicability (Hulsurkar et al., 2021). Other genetic mouse models related to potassium channel mutations, sodium channel mutations, and sarcoplasmic reticulum (SR) Ca^{2+} leak have also been utilized for AF studies (Temple et al., 2005; Li et al., 2009, 2012, 2014; Blana et al., 2010; Guzadhur et al., 2010; Watanabe et al., 2011).

Inflammation and AF may be related, as AF has been observed to occur in numerous rodent models of various inflammatory diseases (Ajoolabady et al., 2022). The NACHT, LRR, and PYD domain-containing protein 3 (NLRP3) inflammatory vesicle activity was reported to be enhanced in atrial cardiomyocytes of AF patients undergoing atrial tachypacing (ATP) and ATP dogs (Yao et al., 2018). The cardiomyocyte (CM)-restricted activation of NLRP3 in mice promotes ectopic firing and maintenance of AF substrates, ultimately leading to AF (Yao et al., 2018). Post-operative atrial fibrillation (POAF) is characterized by the onset of AF 1–3 d after surgery, and mice that have undergone cardiothoracic surgery were shown to exhibit a greater induction of AF (38.4%) (Keefe et al., 2022). The occurrence of atrial remodeling and AF arrhythmia was evaluated in a rat model of left ventricular radiofrequency ablation-induced heart failure (Nofi et al., 2020; Shen et al., 2022; Ma et al., 2023). Compared to mice without chronic pain, specimens with chronic pain were noticeably more vulnerable to AF induced by thoracic electrical bioimpedance (TEB) pacing, which was supported by electrophysiological findings: longer pulse rate (PR) interval, which indicates slower atrial conduction, and shorter atrial effective refractory period (AERP) (Gong et al., 2022).

The classical concept focused on the M2 muscarinic acetylcholine receptor (M2 receptor (M2R)) and it signaling cascade, which includes regulator of G protein signaling 4 (RGS4), as these had been shown to exert predominant effects on nodal function (heart rate and conduction block) as well as on contractility, even though it has been known for more than fifty years that cholinergic stimulation can initiate AF (Alessi et al., 1958; Liu and Nattel, 1997). RGS2, a putative regulator of the M3 receptor, may be a target for therapeutic intervention (Jones et al., 2012); emerging evidence suggests that the M3 receptor may also contribute to the onset and maintenance of AF (Hellgren et al., 2000). RGS2-deficient ($RGS2^{-/-}$) mice had dramatically changed electrophysiological atrial responses and were more prone to electrically induced AF (Jones et al., 2012).

Rats are similar to mice in many ways, including their benefits and drawbacks in AF models, but they also possess special qualities that mice do not. The strong increase in AF susceptibility associated with significant right atrial (RA) remodeling in the right heart disease (RHD) rat model suggests the importance of RHD as an AF-inducing condition (Hiram et al., 2019). Sterile pericarditis (SP) rats exhibit marked Ca^{2+} mishandling and Ca^{2+} treatment heterogeneity, as well as increased susceptibility to Ca^{2+} transient (CaT) and action potential duration (APD) alternations (especially spatially inconsistent alternations) induced by delayed CaT under duration, which is causally related to enhanced AF inducibility (Liao et al., 2021). Rats with radiofrequency-induced heart failure presented significant atrial structural changes (dilatation and interstitial fibrosis) and enhanced AF vulnerability compared to controls (dos Santos et al., 2018). The acetylcholine-$CaCl_2$-induced AF rat model has often been used to study AF, and a variety of drugs could improve heart function under this model (Chen et al., 2016; Feng et al., 2023). AF brought on by exercise

may be sympathetically triggered (Linz et al., 2014). The vagal promotion mechanism, which is mediated by improved baroreflex responsiveness and heightened cardiomyocyte sensitivity to cholinergic stimulation, increases AF susceptibility in rats with persistent endurance exercise (Guasch et al., 2013). Obesity and acute obstructive sleep apnea (OSA) have also been associated with AF (Iwasaki et al., 2012). During obstructive apnea, AF was generated in 24 of 28 obese rats (ORs) (85.7%) compared to 5 of 18 lean rats (LRs) (27.8%) (P<0.01). Left ventricular hypertrophy and diastolic dysfunction were detected by echocardiography in ORs. Acute left atrium (LA) dilatation brought on by obstructive apnea increased the LA diameter substantially more in ORs than LRs (Iwasaki et al., 2012).

2.2 Cats

Cats have been rarely used as animal models for AF studies, and the only relevant literature available focuses on the effects of aconitine on AF (Ammar and Kudrin, 1969; Gendenshteĭn and Kostin, 1976; Gendenshteĭn et al., 1976, 1977; Byrne et al., 1977; Winslow, 1981). The first study on the effects of aconitine on heart rate was conducted in 1969 (Ammar and Kudrin, 1969). Subsequently, Byrne et al. (1977) succeeded in inducing AF in cats (3/5 were induced). Winslow (1981) successfully induced supraventricular arrhythmias in cats, including AF, by the topical administration of aconitine. In addition, this model proved to be more effective than the previous one and was also often used to test antiarrhythmic drugs (Gendenshteĭn and Kostin, 1976). Besides, left atrial dilatation during hypertrophic cardiomyopathy in cats also predisposes to AF (Gendenshteĭn et al., 1977).

2.3 Guinea pigs and rabbits

In terms of cellular electrophysiology, guinea pigs and rabbits are more comparable to humans than mice and rats, with the action potential showing the most noticeable difference. The hearts and cardiomyocytes of guinea pigs and rabbits are particularly well suited for researching cardiac repolarization because of this unique trait. Few guinea pig AF models are available despite the fact that many ventricular electrical investigations utilizing guinea pig hearts have been carried out.

In the Langendorff model of acutely induced AF in the guinea pig heart, small-conductance Ca^{2+}-activated K^+ (SK) channel blockers in combination with multiple drugs maintain anti-AF properties while reducing the risk of ventricular arrhythmias (Diness et al., 2015; Kirchhoff et al., 2015, 2016). As a result of a decrease in Ca^{2+} current (I_{Ca}) and an increase in K^+ current (I_K), the APD shortens in septic guinea pig atrial myocytes. The nitration of ion channels rather than changes in atrial expression of the ion channels appears to be responsible for these electrophysiological abnormalities (Aoki et al., 2012).

In a rabbit model with arteriovenous shunts, conduction slowing was observed, and atrial tachyarrhythmias were linked to foldback and localized stimulation coming from the posterior LA (Torii et al., 2021). Enhanced atrial pressure caused effective refractory period (ERP) shortening and increased AF vulnerability in isolated rabbit hearts in a model of acute atrial damage (Lequerica et al., 2009). Rabbits presented significant left atrial fibrosis and a significant increase in atrial conduction heterogeneity and AF susceptibility after four weeks of rapid atrial pacing (RAP) treatment (Aidonidis et al., 2021a), whereas drug treatment significantly reduced atrial remodeling and AF susceptibility (Fan et al., 2019; Aidonidis et al., 2021b). As seen in the rabbit ventricle, β-stimulation also elevated atrial diastolic intracellular Ca^{2+} (Nogami et al., 2003) and might have enhanced a diastolic Ca^{2+} SR leak (Danson et al., 2005; Curran et al., 2007). In 2021, the question of whether cellular electrophysiology would extend to AF was explained. By comparing the echocardiography, atrial electrophysiology, oxidative stress, and mitochondrial function in different groups, Zhou et al. (2021) could explain the mechanisms of AF in diabetes mellitus.

The data gathered from small animal models of AF show that there are obvious limitations to using such models for AF; therefore, AF needs to be further investigated in large mammals. Programmed electrical stimulation is first needed to induce AF onset, for short durations of only a few seconds each. Notably, tiny animal models have indicated the crucial role of supporting putative signaling pathways that may result in human AF, despite the fact that they do not exhibit the pathophysiological abnormalities seen in human AF. The advantages and disadvantages of different species of small animal models are shown in Table 1.

Table 1 Advantages and disadvantages of different species of small animal models

Species	Advantages	Disadvantages
Rats, mice	Easy to generate and manipulate; low rearing costs	Differences in heart size and electrophysiology; tools used for human electrophysiological studies are not applicable to mice
Rabbits, guinea pigs	Pharmacology research; easier to perform experimental manipulations	Weak genetic manipulation; short duration of AF

3 Large animal models of AF

3.1 Dogs

Spontaneous AF can occur in dogs as an independent problem in the absence of other cardiac disease prerequisites. In most cases, AF in large and giant breeds (30−90 kg body weight) is secondary to dilated cardiomyopathy. In small breeds (8–20 kg body weight), AF has been rarely reported. Older dogs and males are at higher risk of developing AF.

Many studies of atrial electrophysiology and AF have been conducted in dogs. The APD of canine portal veins (PVs) is shorter than the peripheral LA due to the reduced the inward rectifier current (I_{KI}) and the altered intercellular coupling, leading to an elevated resting membrane potential (Ehrlich et al., 2003; Sicouri et al., 2019). On the other hand, the canine AF model often uses adenosine triphosphate and has been widely implemented to study cellular electrical remodeling in AF (Nattel and Dobrev, 2016). Because the duration of AF in such animals is generally short, even stimulated for only weeks, and because pharmacological treatment is usually insufficient to prevent tachycardia-induced left ventricular injury, canine ATP is often required for simultaneous rate control by atrioventricular (AV) node ablation (Kato et al., 2014).

Several studies have demonstrated that PV is associated with facilitated AF (Yoo et al., 2023). In dogs with RAP, the PV cardiomyocytes with pacemaker activity have been observed to have a greater incidence of delayed after-depolarization (DAD) or early after-depolarization (EAD) (Chen et al., 2001). There have also been reports of non-iatrogenic localized re-entrant activations in the PVs of a canine model of pacing-induced persistent AF (Zhou et al., 2002). However, atrial tachycardia (AT) in dogs lowers PV-LA action potential discrepancies and causes qualitatively equivalent ionic remodeling in the LA and PVs (Cha et al., 2005), with a reduction in L-type Ca^{2+} current ($I_{Ca,L}$), transient-outward current (I_{to}), slow delayed-rectifier current (I_{Ks}), and an increase in Na^{+}/Ca^{2+} exchanger current (I_{NCX}) (Cha et al., 2004). Additionally, in AT-remodeled LA preparations, the excision of all PVs does not change the inducibility of atrial tachyarrhythmia (Cha et al., 2005). Similar to the rat ventricle, increased I_{NCX} and CaT promote EAD development in superfused canine pulmonary veins. Tachycardia pause causes fast firing within the PV sleeve after acetylcholine has shortened the action potential (Patterson et al., 2006).

In addition to the rapid AT model, heart failure-related AF and vagal tone-induced AF have been utilized in dogs. Congestive heart failure (CHF) induced by five weeks of rapid ventricular pacing (220–240 beats per min (bpm)) prolonged the duration of abrupt pacing-induced AF, a result similar to the one-week effect of RAP. Compared with RAP, CHF did not alter atrial nonresponse, nonresponse heterogeneity, or conduction velocity, but conduction heterogeneity during atrial pacing was significantly increased (Pedro et al., 2020).

Vagus nerve stimulation readily facilitates the induction and maintenance of AF. The advantage of this method is that it is less expensive and produces stable AF induction, and this model has been used for the in vivo screening of potential antiarrhythmic drugs (Goldberger and Pavelec, 1986). Acetylcholine stimulation of the K channel, which stands for APD and ERP, causes vagally mediated AF (Goldberger and Pavelec, 1986). Furthermore, vagal stimulation enhances ERP heterogeneity, which is positively correlated with the length of inducible AF (Wang et al., 1996). Optical mapping tests demonstrated that re-entrant activity was the cause of acetylcholine-induced persistent tachycardias in an ex vivo canine PV sample (Po et al., 2005). The activation of the autonomic ganglia at the base of the right superior PV caused PV firing to transition into AF in anesthetized dogs (Po et al., 2005).

Numerous investigations have demonstrated that AF related with hypoxia involves the autonomic nervous system (ANS) (Zhou et al., 2020; Liu et al., 2021; Han et al., 2023). Excessive vagal tone activation and

the resulting autonomic imbalance in animal models of acute intermittent hypoxia, such as hypoxemia, hypercapnia, and acidosis, are significant factors affecting AF related to hypoxia (Lu et al., 2013). In addition to making up a sizeable portion of intrinsic cardiac ANS (Shen and Zipes, 2014), cardiac GP controls the autonomic interactions between exogenous and intrinsic cardiac ANS and is crucial for the development and maintenance of AF (Scherlag et al., 2008). In a model of 2-min acute apnea, GP ablation in the right pulmonary artery prevented AF (Ghias et al., 2009). According to recent studies, stimulating the epicardial fat pads that contain GP clusters can cause spontaneous AF (Po et al., 2006). AF induction was successfully avoided with radiofrequency GP ablation (Scherlag et al., 2005). The long-term effects of GP ablation on AF are still unclear, despite the fact that long-term vagal denervation of the atria can be accomplished by the radiofrequency catheterization ablation of epicardial fat pads (Chiou et al., 1997). In the study of Oh et al. (2006), radiofrequency fat pad ablation could not permanently prevent AF onset in a canine model.

In a study of therapeutic relevance, Gerstenfeld et al. (2011) examined the processes of complicated AF electrogram grading in AF in ATP dogs that have been identified as possible targets for AF ablation. However, the majority of complex AF electrograms result from wavefront collisions and are not the underlying causes of AF. Complex AF electrograms typically begin posterior to the LA and close to the PV orifice. The absence of structural abnormalities or fibrosis in these areas is significant because it may help to explain why the segmental ablation of complex AF electrograms has no effect (Gerstenfeld et al., 2011). Balkhy et al. (2007) identified the principal epicardial autonomic ganglionated plexi at the junction of the inferior vena cava-main portal vein (IVC-MPV) in a canine model. Epicardial microwave ablation of this GP reduced or eliminated AV block and prolonged AF induction during cervical vagal trunk stimulation. Besides, it also removed the vagal response to local fat pad stimulation (Balkhy et al., 2007). Cholinergic AF was investigated in vitro using carbachol-infused coronary perfused canine left atrial PV preparations and in vivo using cervical vagus nerve stimulation (Lemola et al., 2008). An undamaged ventricular vein is not necessary for the continuation of experimental cholinergic AF. Ventricular vein-focused ablation for vagal AF may be more effective if the autonomic ganglion at the base of the ventricular vein is removed, as this reduces the vagal response (Lemola et al., 2008).

It has been common practice to employ the canine model for AF inflammation, particularly the aseptic pericarditis model (Lee et al., 2022). This model has helped researchers to better understand the causes of AF and atrial flutter as well as how quickly AF might develop (Ortiz et al., 1994). It has also shown a link between postoperative AF and inhomogeneous atrial conduction, which is improved by anti-inflammatory medication (Ortiz et al., 1994). In an SP model, the use of ranolazine prolonged the AERP and AF cycle length in dogs, and stopped acutely generated atrial flutter and AF (Bhimani et al., 2014). After atrial GP ablation in dogs, the inflammatory response in the atria increases. Although the autonomic influence is abolished, the rise in atrial inflammatory components may reveal novel causal elements in the vulnerability to AF (Zhao et al., 2011).

A canine atrial ischemia model was also developed, and AF was facilitated by remodeling brought on by atrial acute myocardial infarction (Wada et al., 2021). After atrial infarction, the AERP remained unaffected; however, conduction velocity was decreased (Rivard et al., 2007). Moreover, spontaneous Ca^{2+} and I_{NCX} levels rose in response to changes in calcium homeostasis (Gussak et al., 2020). Interestingly, heat shock protein induction prior to atrial ischemia delays the onset of AF caused by ischemia. This is because heat shock protein induction reduces oxidative stress following acute myocardial infarction (Wang et al., 2018). In a canine AF model that included ventricular infarction, a cured infarct model produced numerous waves, caused inhomogeneity in atrial monophasic APD, and increased the frequency and length of pacing-induced AF (with a mean of 41 s) (Miyauchi et al., 2003). Dogs were used in the study of chronic myocardial infarction, and the model revealed a decrease in atrial Cx40 and an increase in abrupt atrial pacing (episode duration ranging from 20 s to 1 min) (Ohara et al., 2002).

3.2 Pigs

As a large animal, the pig is able to simulate some chronic diseases very well. In anatomical and physiological terms, pigs, especially small breeds, have similar organ sizes and functions to humans and comprise good model animals for constructing human

disease models. This being said, there are no reports of spontaneous AF in pigs.

The pig AF model was originally developed using aseptic pericarditis by Schwartzman et al. (2016). Therein, AF was indeed increased from 10% immediately following surgery to 80% one week later. The Aachener small pig aseptic pericarditis-induced atrial myopathy model was created by Tubeeckx et al. (2021), which was characterized by AF inducibility, the fast induction of inflammation and fibrosis, and repeatability. The first porcine model of acute AF was established in 2016, and almost all animals therein sustained AF without pharmacological intervention (Lee et al., 2016).

Atrioventricular nodal blockade can be utilized to lessen or stop the development of systolic dysfunction, which increases the usefulness of ATP-induced AF pigs. Schwarzl et al. (2016) employed subcutaneous deoxycorticosterone acetate to induce hypertension in the model, which was able to accelerate atrial remodeling and enhance the persistence of AF, though mortality was increased in the conditioned animals. They used digoxin for nodal blockade to produce AF episodes lasting longer than 60 min without signs of CHF (Schwarzl et al., 2016). Similarly, Lin et al. (2003) were able to produce AF for more than 24 h using digoxin in addition to six weeks of ATP. Pigs with investigator-defined sustained AF exhibited AERP prolongation, pronounced changes in cellular Ca^{2+} homeostasis, and upregulation of the Na^{+}/Ca^{2+} exchanger at the expense of downregulations of protein kinase A, calcium/calmodulin-dependent protein kinase II (CaMKII) subunit δ, sarco/endoplasmic reticulum Ca^{2+}-adenosine triphosphatase (ATPase) 2a (SERCA2a), ryanodine receptor 2 (RyR2), and the L-type Ca^{2+} channel (Lugenbiel et al., 2015). Quintanilla et al. (2019) employed a crossbred pig strain to control development and a dual-chamber pacemaker that delivered ATP and ventricular pacing to accomplish atrioventricular node ablation (60–100 bpm). In this model, persistent AF developed over a median of 4.4 months with LA dilatation and ATP stimulation, but there was no change in LV systolic function (Quintanilla et al., 2019).

Increased vagal tone is one of the mechanisms, by which endurance exercise is linked to an increased risk of AF. Acetylcholine or epinephrine induced AF with or without pacing to evaluate the effects on autonomic functions (although only short episodes of a few minutes) (Justo et al., 2016). The model blocked the late sodium channel (Na^{+} current (I_{Na})) to prevent AF (Namekata et al., 2022). This channel has drawn a lot of attention due to its importance in ischemia- and vagal-related AF in pigs (Manati et al., 2018; Godoy-Marín et al., 2023).

The antiarrhythmic effects of SK channel blockers have been the most intensively studied AF-related topic in pigs. Diness et al. (2017) showed that, in pigs with rapid tachypacing for 7 d, the SK channel blocker AP14145 shortened AF duration in a dose-dependent manner and AERP was significantly prolonged. Another SK channel blocker, AP30663, extended the AERP in a dose-dependent manner by ⩾30 ms even at the lowest dose, which was considered sufficient to prolong cardioversion AF in pigs (Diness et al., 2020). Treatment with the most commonly available potassium two-pore domain channel subfamily K member 3 (KCNK3, TASK-1) inhibitor, A293 (AVE1231), reversed AF-induced action potential shortening and prolonged AERP independent of ventricular function in pigs induced with AF for 14 d (Wiedmann et al., 2020). Other drugs, such as amiodarone, prolonged the ERP and reduced the rate of acutely induced AF and atrial flutter in pigs (Garcia et al., 2018). The use of ranolazine in pigs not only selectively increased the AERP without influencing the ventricular ERP (vERP) but also reduced the duration of acutely induced AF (Kirchhoff et al., 2015; Saljic et al., 2022).

3.3 Goats and sheep

The most frequently used large animals for AF models are goats and the smaller-sized sheep (20–150 kg body weight). Thus far, no spontaneous AF has been reported in goats or sheep, but these animals have been observed to have sinus arrhythmias and secondary and tertiary AV block.

Wijffels et al. (1995) first reported that persistent AF in a goat model altered atrial electrophysiology, thereby enhancing susceptibility to and persistence of AF. Therein, they used the term “atrial remodeling” for the first time to describe the changes in the promotion of AF caused by AF itself. AF-induced remodeling is virtually indistinguishable from any rapid AT-induced remodeling, which is referred to as AT-induced remodeling.

Congestive heart failure is one of the most common clinical causes of AF, and this model has been

explored in goats. In a sheep model with congestive heart failure, AF frequency was affected (Takemoto et al., 2017; Frydrychowski et al., 2020). The slow-going AV block triggered by four weeks of induction in goats resulted in progressive atrial dilatation and prolonged AF, in which the AERP or AF cycle was unchanged but local conduction delays occurred during rapid pacing (Pruvot et al., 2007). In a goat aortic-LA shunt model, ERP prolongation and AF duration were increased (Remes et al., 2008). A model of aseptic pericarditis exhibited ERP shortening and reduced frequency adaptation accompanied by increased susceptibility to AF (Zhang et al., 2015). Cardiac-specific overexpression of transforming growth factor-β1 (TGF-β1) resulted in structural changes in AF, including P-wave prolongation and increased susceptibility to AF (Polejaeva et al., 2016).

Aorto-pulmonary shunts in sheep predispose the atria to AF electrophysiological and structural remodeling, indications of cellular inexcitability, myolysis, and myocyte hypertrophy, including a triangular action potential shape brought on by decreased $I_{Ca,L}$ (Deroubaix et al., 2004). Moreover, prenatal corticosteroid-induced hypertensive sheep show increased LA enlargement and AF duration (Kistler et al., 2006). Shorter AERPs, a decrease in $I_{Ca,L}$, and altered CaTs are among the effects of intermittent ATP (for example, for 4 h at 900 bpm), and these changes increase AF vulnerability (Lenaerts et al., 2011; Monigatti-Tenkorang et al., 2014). Besides, shorter APD and lower I_{Na} and $I_{Ca,L}$ are also signs of electrical remodeling (Martins et al., 2014).

3.4 Horses

The first electrocardiogram (ECG) of AF in horses was reported by Lewis (1911). Since then, AF has been reported in a variety of horse breeds, but not ever in ponies (100–350 kg body weight). The percentage prevalence of AF in large horses was between 0.29% and 2.50%, with the highest value in warmblooded horses (500–700 kg body weight) and standardbred large-head horses (450–600 kg body weight) (Ramírez and Tinker, 2021; Kjeldsen et al., 2022). AF in a paroxysmal form is considered to occur frequently in horses (Buhl et al., 2021).

Horses are considered to provide excellent large animal models for exploring structural and electrical remodeling as well as drug studies, not only because they have a similar AF phenotype to humans but also because they feature more PVs and a larger body size than humans (Carstensen et al., 2019; Linz et al., 2020). It has been shown that ATP-stimulated horses, with enhanced atrial fibrosis in the presence of prolonged AF, exhibit an AF phenotype similar to that of humans (de Clercq et al., 2008; Hesselkilde et al., 2019). Hesselkilde et al. (2019) found that persistent AF with left atrial dilation and left atrial contraction occurred in 5/6 horses stimulated with ATP for three weeks. Carstensen et al. (2018, 2019) investigated the electrophysiological effects of ranolazine and the combination of ranolazine and dofetilide in an induced AF horse model. In 25% of horses, ranolazine cardioverted acutely induced AF, and this rate increased to 75% when ranolazine was combined with dofetilide. In 2020, local electrograms in sinus rhythm were reported, and then spontaneous pulmonary vein firing and a brief, non-persistent run of AF were observed (Linz et al., 2020). Without manipulating the catheter, and both before and after the catheter was removed, brief bursts of fast atrial activation were seen in horses. The advantages and disadvantages of different species of large animal models are illustrated in Table 2.

In order to help researchers better choose the appropriate animal model, we summarized the existing animal models and their modeling approaches in Table 3. In addition, the different types of AF and their main mechanisms and common animal models were summarized in Table 4.

4 Advances in AF treatment

4.1 Current clinical treatments

Providing effective treatment options for AF remains a major challenge, and the current treatments of human AF mainly include radiofrequency ablation surgery, together with antiarrhythmic drugs such as ion channel blockers and additional anticoagulant drugs to prevent possible complications (Arbelo and Dagres, 2022; Calvert et al., 2022). Recent reports on catheter ablation versus pharmacotherapy in AF suggest that catheter ablation has a better performance in terms of cost-effectiveness and treatment outcome, especially for younger patients (Packer et al., 2021; Bahnson et al., 2022; Chew et al., 2022).

Table 2 Advantages and disadvantages of different species of large animal models

Species	Advantages	Disadvantages
Goats	Long duration	Relatively short action potential
Dogs	Ability to use clinical instruments; anatomy and electrophysiology similar to human	Complex genetic background; significant differences in heart weight/body weight ratio; electrocardiographic differences; low social acceptance
Sheep	Classical AF model	High feeding costs; low similarity to human physiology
Pigs	Heart and coronary artery structure similar to human; electrophysiology similar to that of human; action potentials similar to human; gene editing is possible	Few coronary artery side branches
Horses	Natural development AF; AF follows a similar progression to that of human; PV has ectopic electrical activity that can trigger AF	Electrophysiological properties are different from those of human; different action potentials have different durations; high feeding costs; low social acceptance

AF: atrial fibrillation; PV: portal vein.

Drug therapy cannot eradicate AF but can provide some therapeutic and preventive effects. Current medications used to treat AF include anticoagulant therapy drugs, drugs to revert and maintain sinus rhythm, and drugs to control ventricular rate.

Pulmonary vein isolation is the basis of current AF ablation techniques (Erhard et al., 2022). Treatment by this technique with a certain period of postoperative drug therapy has been shown as effective in patients with paroxysmal AF. However, in patients with long-term persistent AF, the structures that trigger AF are not limited to the pulmonary veins but include the coronary sinus, the left auricle, the superior vena cava, the terminal cleft muscle, and so on, which prompts the exploration of further ablation techniques for patients with long-term persistent AF. The current ablation techniques include pulmonary vein isolation, linear ablation of the mitral valve, and ablation of the right atrium.

In another approach, the cardiac system is disturbed by optogenetic techniques to control different types of cardiac myocytes to achieve cardiac pacing, defibrillation, or resuscitation. Compared with the conventional clinical treatment of AF, optogenetic techniques can terminate heart rate arrhythmias while avoiding drug side effects or tissue damage (Bingen et al., 2014). The reversible and non-invasive nature of optogenetic technology has attracted increasing attention in the treatment of arrhythmias, but its future application in the clinic still requires extensive experimental studies.

4.2 Experimental treatments in animal AF models

In common animals such as dogs and cats, AF is often diagnosed via ECG, and the principles of pharmacological treatment are divided into two main categories: heart rate control, which slows down the ventricular heart rate without converting AF to sinus rate, and cardioversion, which converts AF to sinus rate (Zhao et al., 2022). Treatment options are chosen by the severity of clinical symptoms, and rhythm control is generally avoided if the condition is more severe. Commonly used medications for rhythm control include calcium channel blocker (CCB), digoxin, β-blocker (BB), and potassium channel blocker (PCB). These drugs often achieve better efficacy when combined. In cardioversion, antiarrhythmic drugs are generally used, and intravenous amiodarone is the treatment of choice in canine sudden-onset AF. Oral amiodarone is also effective, while the success rate of cardioversion is relatively low (Oyama and Prosek, 2006). Currently, amiodarone is widely used as a relatively safe and mild drug in the clinical management of humans. In a comparative study on the efficiency and safety of drug conversion in the treatment of AF, procainamide, propafenone, and amiodarone were all effective in restoring sinus heart rate, whereas amiodarone and propafenone were more effective, with procainamide and propafenone having a faster onset of action (Kochiadakis et al., 2007).

In terms of surgical treatment, the most commonly employed technique in dogs is biphasic transthoracic cardioversion; in exceptional cases, intracardiac and transesophageal cardioversions are generally chosen as alternatives, a protocol that has been practiced in research animals but is less common in veterinary practice. In addition, there have been cases of transvenous electrical resuscitation (Jung et al., 2017).

Additional novel drugs are also currently being used in various animal models of AF and have been

Table 3 Summary of existing methods and mechanisms in atrial fibrillation (AF) animal models

Species	Method	Mechanism
Mouse	Transgenic	Gene editing
	Inflammation	Inflammation-related
Rat	Spontaneous	Inflammation-related
	Hypertensive	Inflammation-related
	Asphyxia	Changes in autonomic tone
	Ventricular ischemia	Inflammation-related
	Pulmonary hypertension	RA fibrosis and conduction abnormalities
Guinea pig	Aconitine perfusion	Acetylcholine receptor-operated K^+ (KACh) channel-related
Rabbit	ACh infusion	Increase AERP and prolong the APD
	ATP for 4 weeks	Atrial fibrosis
Goat	ATP for 48 h or 6 months	Electrophysiological changes
	CAVB	Chronic AV block
	Volume overload	Chronic aortic to left atrial shunt
	Sterile pericarditis	Inflammation-related
	TGF-β1 overexpressing	Progressive atrial fibrosis
Dog	Spontaneous AF	Spontaneous
	ATP for 24 h/3 weeks/6 weeks	Atrial tachycardia/autonomic activation/chronic nonvalvular AF
	VTP for 2 weeks	Congestive heart failure
	ACh+isoproterenol infusion	Changes in autonomic tone
	Sympathetic denervation	Heterogeneous sympathetic atrial denervation
	MR+ATP for 6 weeks	Spontaneous
	Atrial ischemia	Coronary artery disease
	Ventricular ischemia	Atrial electrical and neural remodeling
	Sterile pericarditis	Inflammation-related
	Periodontitis	Inflammation-related
Sheep	ATP	Spontaneous after ATP discontinuation
	ATP for 2–5 s every 2–5 s over 4 h	
	ATP for 13 weeks/around 40 d	
	Aged sheep	APD alternans
	VTP for 4–6 weeks	Heart fibrosis
	Volume overload	Spontaneous
	Atrial ischemia	Left ventricular infarction
	Vagal stimulation	Electrophysiology
	Prenatal corticoids	Blood pressure
	Unilateral nephrectomy and contralateral clamping	Hypertension
	High-calorie diet (8 weeks)	Sustain obesity
Pig	ATP for 1–6 weeks/2 weeks/6 weeks	Atrial remodeling/gene therapy/chronic AF
	ATP for months+AVN ablation	Persistent atrial fibrillation ablation
	ACh+infusion	Local atrial repolarization
	MR	Mitral regurgitation
	Ventricular ischemia	Atrial arrhythmogenicity
Horse	Spontaneous AF	Spontaneous
	Healthy horses	Antiarrhythmic drug
	ATP for 2 s every 4 s over 4 weeks	Chronic AF

ACh: acetylcholine; AERP: atrial effective refractory period; APD: action potential duration; ATP: atrial tachypacing; CAVB: chronic atrioventricular block; AV: atrioventricular; TGF-β1: transforming growth factor-β1; VTP: ventricular tachypacing; MR: magnetic resonance.

shown to have some therapeutic effects. In the prevention of AF, anticonvulsant valproic acid (a histone deacetylase inhibitor) has been reported to weaken atrial fibrosis and slow the spontaneous onset of AF in a transgenic mouse model, which may be a new treatment option for AF prevention. Due to the link between inflammation and AF, Calvo et al. (2018) concluded that the potent anti-inflammatory effects of corticosteroids may be valid for AF in animals, while Pinho-Gomes et al. (2014) suggested that the

anti-inflammatory, anti-oxidant, and membrane stabilizing properties of statins may contribute to the prevention of AF-induced electrical remodeling in an animal model of AT and decrease the recurrence of AF after cardiac surgery. Other drugs, such as pirfenidone and trenbolone, have been shown to reduce structural and electrical remodeling and prevent vulnerability in canine models of AF; however, relevant clinical studies are still lacking. In a more promising future outlook, preventive genetic breeding strategies in dog breeds known to be genetically predisposed to AF will be considered, possibly even providing a more "personalized" genotype-directed treatment approach. In Table 5, we summarize the application of commonly used antiarrhythmic drugs in large animal models.

5 Summary

Animal models are extremely important for the study of human AF, both in terms of mechanism and treatment. Currently, most research on treatment options for human AF is carried out on animal models. However, the differences in cardiovascular systems between the various types of animals and those between animals and humans lead to the numerous limitations of animal models, with the non-uniformity of AF mechanisms adding to these shortcomings in the establishment of each model. The accessibility and ease of manipulation of small animals make such models easier to establish, though the cardiovascular systems of small animals differ more from those of humans than from those of larger animals. The presence of spontaneous AF in large animals makes them more suitable for AF models; however, the current operational techniques in large animals are inferior to those in small animals, and the accessibility and affordability of large animals are also lower, making the establishment of such models and the monitoring of data difficult. Currently, AF in animals is mainly induced by clinical means such as food and drugs, while fewer animal models are established by means of gene mutations. Additionally, the exploration of mechanisms and treatment options at the genetic level has been insufficient. The means to construct suitable animal models, how to use them, and the techniques to

Table 4 Main mechanisms of different types of atrial fibrillation (AF)

Type of AF	Main mechanism	Animal model
Pulmonary vein-dependent AF	PV ectopy; AF trigger	Horse, sheep
Heart failure-associated AF	Low ejection fraction; electrical/structural remodeling; AF substrate	Pig, dog, sheep
Genetic AF	Structurally healthy atria; increased genetic risk; mechanisms unclear	Mouse
Valvular AF	Pressure/volume overload; structural remodeling; AF substrate	Pig, dog, goat, sheep
Inflammation-associated AF	Inflammation; electrical/structural remodeling; AF substrate	Goat, dog
Toxic AF	(1) Cellular toxicity, autonomic imbalance; AF trigger (2) Cellular toxicity, autonomic imbalance; electrical/structural remodeling; AF substrate	Pig

PV: pulmonary vein.

Table 5 Application of common antiarrhythmic drugs in large animal models

AAD	Primary target	Secondary targets	Species
Ranolazine	I_{Na} (late)	I_{Kr}, $I_{Ca,L}$, RyR2	Horse, goat, pig, dog
Flecainide	I_{Na}	$I_{Na,L}$, I_{Kur}, I_{Kr}, $I_{K,ACh}$, $I_{K,ATP}$, I_{to1}, RyR2	Horse, goat, pig, dog
Amiodarone	I_{Kr}	I_{Na}, $I_{K,ACh}$, I_f, $I_{Ca,L}$, I_{K2P}, αAR, βAR, M2R	Horse, goat, pig, dog
Dofetilide	I_{Kr}		Horse, goat, pig, dog
Vernakalant	I_{Kur}	I_{Na}, $I_{K,ACh}$, I_{Kr}, I_{K2P}	Horse, goat, pig, dog
$I_{K,ACh}$ blockers	$I_{K,ACh}$		Horse, goat, pig, dog
$I_{SK,Ca}$ blockers	$I_{SK,Ca}$	I_{Na}, I_{Kr}	Horse, goat, pig, dog
I_{K2P} blockers	I_{K2P}		Horse, goat, pig, dog

AAD: antiangiogenic drug; I_{Na}: Na^+ current; I_{Kr}: rapid delayed rectifier K^+ current; I_{Kur}: ultra-rapid component of the delayed rectifier K^+ current; $I_{K,ACh}$: acetylcholine (ACh)-activated current; $I_{SK,Ca}$: Ca^{2+}-activated K^+ (SK) depolarizing Ca^{2+} channel; I_{K2P}: leak current mediated by the family (K2P) channel; $I_{Ca,L}$: late Ca^{2+} current; RyR2: ryanodine receptor 2; $I_{Na,L}$,: late Na^+ current; $I_{K,ATP}$: atrial tachypacing (ATP)-sensitive current; I_{to1}: rapidly activating and inactivating transient outward current; I_f: hyperpolarization-activated cyclic nucleotide-gated (HCN) channel; αAR: α-adrenergic receptor; βAR: β-adrenergic receptor; M2R: M2 receptor.

develop suitable treatment protocols for human AF, given the differences among different animal models, need to be further elaborated.

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Author contributions

Qian GONG and Xuan LE wrote and edited the manuscript. Pengcheng YU revised and proofread the manuscript. Lenan ZHUANG provided supervision and financial support. All authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Qian GONG, Xuan LE, Pengcheng YU, and Lenan ZHUANG declare that they have no conflict of interest.

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