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Chronic atrial fibrillation causes left ventricular dysfunction in dogs but not goats: experience with dogs, goats, and pigs

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Dosdall DJ, Ranjan R, Higuchi K, Kholmovski E, Angel N, Li L, MacLeod R, Norlund L, Olsen A, Davies CJ, Marrouche NF. Chronic atrial fibrillation causes left ventricular dysfunction in dogs but not goats: experience with dogs, goats, and pigs. *Am J Physiol Heart Circ Physiol* 305: H725–H731, 2013. First published June 28, 2013; doi:10.1152/ajpheart.00440.2013.—Structural remodeling in chronic atrial fibrillation (AF) occurs over weeks to months. To study the electrophysiological, structural, and functional changes that occur in chronic AF, the selection of the best animal model is critical. AF was induced by rapid atrial pacing (50-Hz stimulation every other second) in pigs ($n = 4$), dogs ($n = 8$), and goats ($n = 9$). Animals underwent MRIs at baseline and 6 mo to evaluate left ventricular (LV) ejection fraction (EF). Dogs were given metoprolol (50–100 mg po bid) and digoxin (0.0625–0.125 mg po bid) to limit the ventricular response rate to <180 beats/min and to mitigate the effects of heart failure. The pacing leads in pigs became entirely encapsulated and lost the ability to excite the heart, often before the onset of sustained AF. LV EF in dogs dropped from 54 ± 11% at baseline to 33 ± 7% at 6 mo ($P < 0.05$), whereas LV EF in goats did not drop significantly (69 ± 8% at baseline vs. 60 ± 9% at 6 mo, P = not significant). After 6 mo of AF, fibrosis levels in dog atria and ventricles increased, whereas only atrial fibrosis levels increased in goats compared with control animals. In our experience, the pig model is not appropriate for chronic rapid atrial pacing-induced AF studies. Rate-controlled chronic AF in the dog model developed HF and LV fibrosis, whereas the goat model developed only atrial fibrosis without ventricular dysfunction and fibrosis. Both the dog and goat models are representative of segments of the patient population with chronic AF.

animal models; chronic atrial fibrillation; fibrosis; heart failure; rapid atrial pacing

ATRIAL FIBRILLATION (AF) is the most frequent chronic arrhythmia (22) and significantly increases the risk of stroke and mortality (7). AF currently affects ~3 million patients in the United States alone, and its prevalence is predicted to increase to >7.5 million by the year 2050 (20). Despite significant advances in treatment options, including rhythm and rate control techniques, AF is frequently recurrent and persistent.

A significant limitation in the development of broadly effective treatments for AF is that the development of the substrate that leads to longstanding persistent AF is not well understood. It is well known that "AF begets AF," or, in other words, the longer AF persists, the more likely it is that a patient will experience more AF in the future (30). Numerous studies (1, 8, 24, 29, 33, 34) have demonstrated that there are significant structural and electrophysiological substrate changes that accompany chronic AF.

Recent studies (14, 15, 26, 27) have shown that whereas electrical remodeling and sustained AF may be achieved in a matter of weeks, tissue levels and structural remodeling continue over months. Patients with longstanding persistent AF exhibit different activation patterns and have higher AF recurrence rates than patients with paroxysmal AF (11, 25, 31). Chronic large animal models of sustained AF provide the opportunity to study the development of the substrate that leads to AF persistence and recurrence. The purpose of this study was to conduct a side-by-side comparison of rapid atrial pacing (RAP)-induced chronic AF in dogs, goats, and pigs. Understanding the advantages and disadvantages of each of these models will enable researchers to select the model that is most appropriate to meet their specific study aims.

METHODS

All animals were managed in accordance with the *Guide for the Care and Use of Laboratory Animals* (12a), and the protocol was approved by the Institutional Animal Care and Use Committee of the University of Utah.

Animals. Yorkshire pigs ($n = 4$, 39 ± 3 kg), mixed breed hounds ($n = 8$, 25 ± 6 kg), and Boer and mixed breed goats ($n = 9$, 37 ± 7 kg) were implanted with pacemakers, and AF was induced with RAP. Additionally, control canines ($n = 6$) and goats ($n = 4$) were used for histological comparison of fibrosis levels.

Pacemaker implantation and programming. Animals received unlimited water but no food for 12- 24 h before surgery and MRIs. Pigs were initially anesthetized with 4.4 mg Telazol/kg im, 2.2 mg ketamine hydrochloride/kg im, and 2.2 mg xylazine hydrochloride/kg im. Dogs and goats were anesthetized with propofol (5–8 mg/kg iv). Animals were intubated and maintained with inhaled isoflurane dosed to effect (1.5–4%) in inspired O_2 under positive pressure ventilation. In goats, an orogastric tube (S-50-HL, 1/2-in. inner diameter, 3/4-in. outer diameter, Tygon Tubing) was advanced into the rumen to evacuate gas and prevent bloat. A subcutaneous pocket on the lateral neck was made, and a neurostimulator (Itrel 3 or InterStim, Medtronic, Minneapolis, MN) was implanted to serve as a pacemaker. A pacing lead (Medtronic) with active fixation was introduced into the right atrium through a jugular vein.

After at least a 1-wk recovery period, pacemakers were programmed to stimulate at 50 Hz with 1 s of stimulation and 1 s without stimulation at two to three times the diastolic pacing threshold. Every 1–2 wk, the ECG was recorded, the ventricular heart rate was measured, the rhythm was evaluated, and the pacemaker was turned off to determine if AF was sustained for a minimum of 20 min. Once AF was sustained, the pacemaker was programmed to stimulate 1 s every minute to reinitiate AF if it spontaneously returned to sinus rhythm.

Drugs. Upon the initiation of pacing, dogs were given metoprolol (50 mg twice daily, oral) and digoxin (0.0625 mg daily, oral) to slow

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the ventricular response rate and the development of heart failure. The ECG was monitored weekly to determine the resting ventricular heart rate, and drug doses were increased up to a maximum of 100 mg twice daily metoprolol and 0.125 mg daily digoxin until the resting ventricular heart rate was <180 beats/min. Daily digoxin and metoprolol doses were continued until the end of the study. Since goats did not exhibit high heart rates or develop significant heart failure, they were not given these medications.

MRIs. At baseline and after 6 mo of AF, MRIs were performed. Animals were anesthetized as during the pacemaker implantation procedures and RAP was terminated. If the animals were in AF, QRS wave-synchronized direct current shocks of progressively increasing energies (200, 300, and 360 J) were given until AF was terminated. MRIs to calculate left ventricular (LV) ejection fraction (EF) were performed 1–2 h after direct current cardioversion, which provides sufficient time for recovery from any cardioversion-induced atrial stunning (13, 16). Four-chamber CINE, LGE, and T1 scans were performed. MRI scans were gated to the ECG, and tracking and correcting for diaphragmatic displacement during the respiratory cycle reduced respiratory artifacts. LV EF was measured with CINE scans.

Histology and quantification of fibrosis. Animals were euthanized at baseline (dogs: $n = 6$, goats: $n = 4$) or after ~6 mo of AF (dogs: $n = 7$, 149 ± 49 days of pacing; goats: $n = 6$, 189 ± 30 days of pacing). Tissue samples were taken from two to eight locations in the right atrium, left atrium, right ventricle, and LV and placed in 10% formalin. Samples were stained with Masson's trichrome. Images to be analyzed were collected from random locations within the samples within the myocardial midwall, avoiding the epicardium and endocardium. Blood vessels and fat were excluded from the analysis.

Images were imported into ImageJ software (free download from the National Institutes of Health). Images were segmented into three colors: red for cardiomyocytes, blue for collagen, and white for other extracellular content. Segmentation was done with the "color segmentation" plug-in. Using the hidden Markov model, each color was sampled at five to eight locations to segment the image into red, blue, and white sections (12). The percentage of the total image that was blue represented the total fibrosis level in the image. Fibrosis levels were quantified for 243 histological samples.

Fibrosis levels were compared for dogs and goats in the atria and ventricles in control animals and after 6 mo of AF using an unpaired Student's *t*-test with P values of <0.05 considered significantly different. Results are shown in Figs. 3–5 as means with bars representing 1 SD.

RESULTS

Pacing and time to sustained AF. Pacemaker implantation was more difficult in pigs due to the depth of the jugular veins and the amount of subcutaneous fat. It tended to be difficult to evaluate an ECG and to program the pacemaker on pigs. To do so, the pigs needed to be anesthetized. They also became agitated upon handling, which made it difficult to determine the resting heart rate. Examining the surgical incisions, drawing blood samples, and evaluating animal health was difficult without sedating the pigs. Pacemaker programming, which also required ECG recording, was not possible without anesthetizing the pigs.

Pigs were given 16 ± 7 days to heal from the pacemaker implantation before the pacemaker was turned on. While the pigs had consistent capture at thresholds < 2 V, the pacing threshold progressively increased such that atrial capture was lost even at the highest settings (10.5 V) 68 ± 39 days after the pacemaker was turned on. Figure 1 shows the encapsulation and fibrosis surrounding an atrial pacing lead in a pig. In pigs, sustained AF was achieved in only two animals after 77 ± 15 days. In the other two pigs, AF was not sustained before atrial capture was lost. Sustained AF was therefore difficult to achieve in the pig model. In the two pigs that achieved sustained AF, one pig died due to heart failure shortly after AF became sustained and one pig died shortly after AF became sustained while under anesthesia for an MRI to evaluate heart function. Therefore, 6 mo of AF were not achieved in any of the pigs in this study.

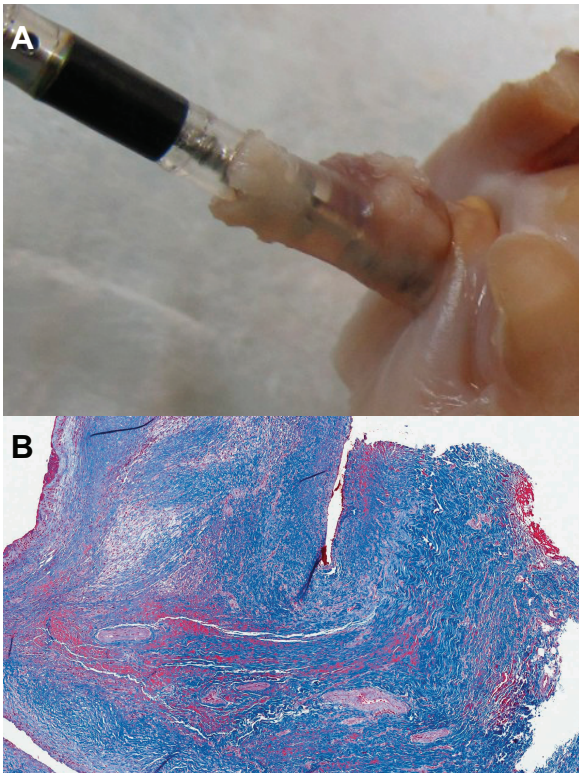

Fig. 1. Encapsulation and fibrotic response to a pacing lead in the right atrial septum of a pig. *A*: pacing lead on the anterior right atrial endocardial surface of a pig 5 mo after pacemaker implantation. The pacing tip has become completely encapsulated and fibrosed in place. The encapsulation of the tip is accompanied by a loss of capture even at maximum pacing voltages (10.5 V). *B*: Masson's trichrome staining of the tissue immediately below the pacing lead showing extensive fibrosis and collagen deposition.

Dogs and goats had consistent capture at pacing thresholds typically <2 V. Consistent atrial capture and low pacing thresholds remained beyond the 6 mo during which these animals were paced. Table 1 shows the ventricular heart rates at various time points during the protocol (means ± SD). Baseline sinus rates were taken during pacemaker implantation (anesthetized) and before pacing initiation (awake). The acute AF heart rate was taken during the 1–2 wk after the initiation of RAP, while the drug dosing in dogs was still being adjusted. The chronic AF heart rate (awake) was taken from an ECG within 2 wk of the 6-mo MRI, whereas the chronic AF heart rate (anesthetized) was taken after the animals had been anesthetized but before cardioversion. The final MRI sinus heart rate was the heart rate during the 6-mo MRI scan. The most elevated heart rates were recorded in dogs shortly after the pacemaker was turned on, which trended toward but did not reach statistical significance ($P = 0.06$ by paired Student's *t*-test). Digoxin and metoprolol doses were increased in any

Table 1. *Ventricular HRs*

	Baseline Sinus Rate		Acute AF HR	Chronic AF HR		6-mo MRI Sinus HR
	Awake	Anesthetized	Awake	Awake	Anesthetized	Anesthetized
Goats	107 ± 34	130 ± 18	141 ± 56	125 ± 40	136 ± 74	109 ± 11
Dogs	123 ± 17	117 ± 25	172 ± 53	130 ± 19	126 ± 38	109 ± 29

Values (in beats/min) are means ± SD. HR, heart rate; AF, atrial fibrillation.

dogs with heart rates higher than 180 beats/min, which resulted in slower heart rates in the awake dogs at the 6-mo time point. Ventricular heart rates were not significantly different for awake and anesthetized animals. Sustained AF developed 69 ± 62 days (range: 10–192 days) and 53 ± 16 days (range: 36–88 days) after the initiation of pacing in dogs and goats, respectively (P = not significant). In both dogs and goats, when sustained AF was detected and the pacing was modified to 1 s/min, the presenting rhythm each of the following rhythm checks was sustained AF and had to be cardioverted with electrical shocks to restore sinus rhythm for the final MRIs.

LV function. Even with a tube in the rumen to evacuate gas from the rumen, bloat was problematic during long MRIs. If bloat was noted, the rumen tube location was adjusted and abdominal compression was performed to evacuate rumen gas. It was not always possible to sufficiently evacuate the rumen. Imaging of bloated goats led to poor MRI image quality due to the cyclical contractions (1–3 times/min) of the rumen. This led to motion of the diaphragm and displacement of the heart. This displacement of 5–10 mm did not coincide with respiratory artifacts. Segmentation of the atrial wall and analysis of atrial dimensions was difficult in the goat model due to poor image quality.

In addition to poor image quality, in ~1/3 of the goat MRI sessions a precipitous drop in heart rate was observed after 3–4 h of anesthesia (Fig. 2). The decline in heart rate was due to atrioventricular (AV) block that began with occasionally blocked beats but progressed within a few minutes to long pauses (>5 s). The development of AV block was not preceded by a drop in sinoatrial node rate or blood pressure. Rescue of the animal required early termination of the MRI scan, administration of emergency drugs [epinephrine (0.5–1.0 ml/50 kg of 1:10,000 dilution) and atropine (0.02–0.04 mg/kg)], and suspension of anesthetic drugs.

Increasing the fasting time for the goats from 12 to 24 h, switching to pelleted feed as opposed to hay to reduce blockage of the rumen gas tube, and positioning the goats in a sternally recumbent position as opposed to lateral or dorsal recumbency reduced the incidence of AV block from ~1/3 of the MRI sessions to ~1/10 of MRI sessions.

Core body temperature was difficult to maintain in dogs and pigs during prolonged MRIs. Animals were covered with blankets, and a recirculating water blanket with adjustable temperature control was used to actively heat dogs and pigs. Goats maintained core body temperature without external heating.

The mean ventricular heart rate in anesthetized animals during sustained AF before MRI scans was 132 ± 41 and 148 ± 56 beats/min for dogs and goats, respectively. LV EF did not change significantly in goats after 6 mo of AF (Fig. 3). LV EF decreased significantly after 6 mo of AF in dogs (Fig. 3), resulting in clinically relevant heart failure by 6 mo despite the use of digoxin and metoprolol. Since 6 mo of AF was not achievable in pigs, data were not available regarding the changes in LV function over time.

Histology. In dogs, the fibrosis level increased significantly in both the atria and ventricles (Fig. 4). In goats, the fibrosis level increased significantly in the atria during 6 mo of AF but did not increase significantly in the ventricles (P = 0.16 for ventricles in goats; Fig. 5).

DISCUSSION

Pigs, dogs, and goats respond differently to the same RAP induction of chronic AF. Table 2 shows the qualitative advantages and disadvantages of each model.

Pigs are widely used as a cardiovascular research model. However, the pig model was the most difficult to implant, monitor, and induce chronic, sustained AF. Even though steroid eluding pacing catheters were used, the pig model demonstrated the problematic tendency to encapsulate the electrodes, leading to the inability to pace the atria and to induce sustained AF. While several studies (6, 17–19) of RAP-induced AF in pigs have been published, none of these reports have models of AF in pigs of >6 wk in duration. There is inconsistency concerning the effect of AF on LV EF and atrial fibrosis in these published studies (see Table 3). A study (6) of RAP-induced AF in which pacing was conducted for 20 days reported that the ventricular response rate was a mean of 274 ± 5 beats/min, which led to the rapid development of

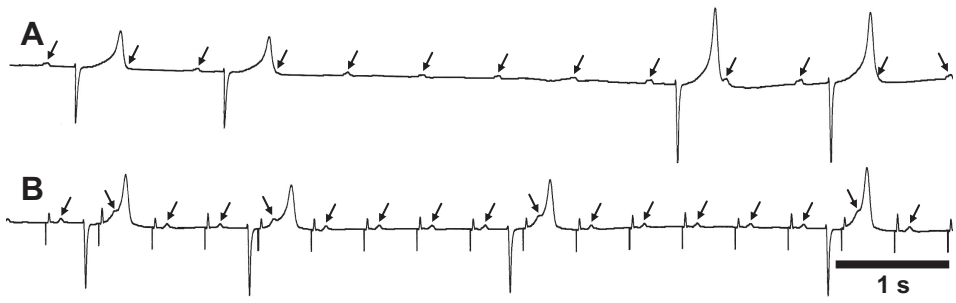

Fig. 2. Development of atrioventricular block in a goat during an MRI. *A*: P-waves (arrows) indicate that the intrinsic sinoatrial rate continued at 90 beats/min, but the atrioventricular node was blocked such that irregular and infrequent ventricular activations occurred. *B*: atrial pacing at 125 beats/min generated P-waves (arrows) but did not cause an increase in the ventricular activation rate. In this case, anesthesia was terminated, atropine and epinephrine were administered, and normal sinus rhythm was restored.

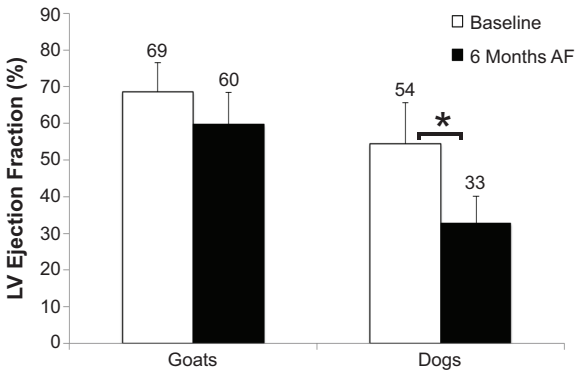

Fig. 3. Goat and dog left ventricular (LV) ejection fraction (EF) at baseline and after 6 mo of atrial fibrillation (AF). Values above bars indicate SDs. *$P <$ 0.05.

congestive heart failure. Dosing pigs with daily medications to reduce the ventricular response rate requires training and significant effort and can be extremely stressful to the animal, although one study (18) reported that oral digoxin resulted in no lowering in LV EF while still observing increases in atrial fibrosis. Our experience and the lack of other studies with chronic AF lasting >6 wk (Table 3) indicates that the pig

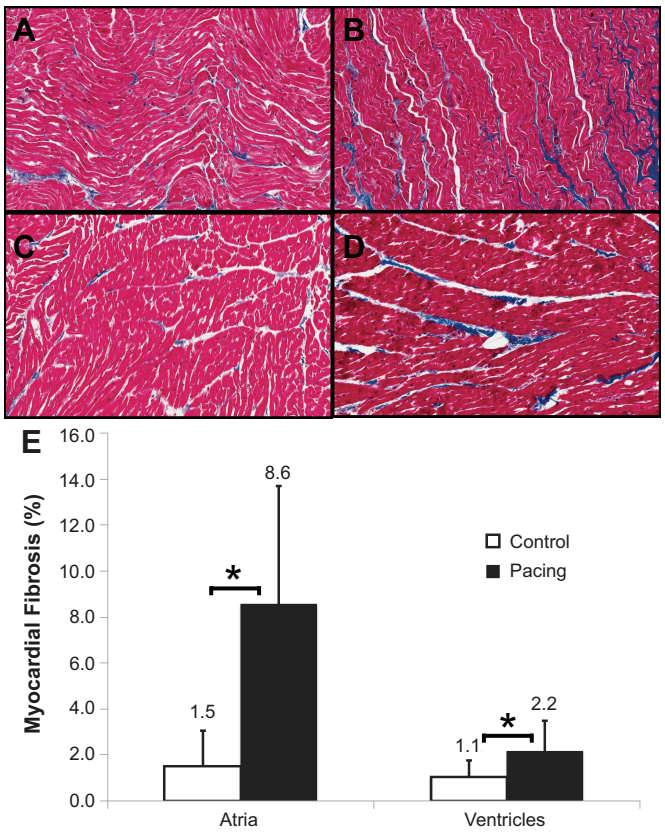

Fig. 4. Fibrosis in the dog model at baseline and 6 mo of AF. *A*: left atrial (LA) sample from a control dog (2.0% fibrosis). *B*: LA sample from a 6-mo AF dog (10.1% fibrosis). *C*: LV sample from a control dog (1.0% fibrosis). *D*: LV sample from a 6-mo AF dog (2.4% fibrosis). *E*: fibrosis levels increased in both the atrial and ventricles during chronic AF. Values above bars indicate SDs. *$P <$ 0.01.

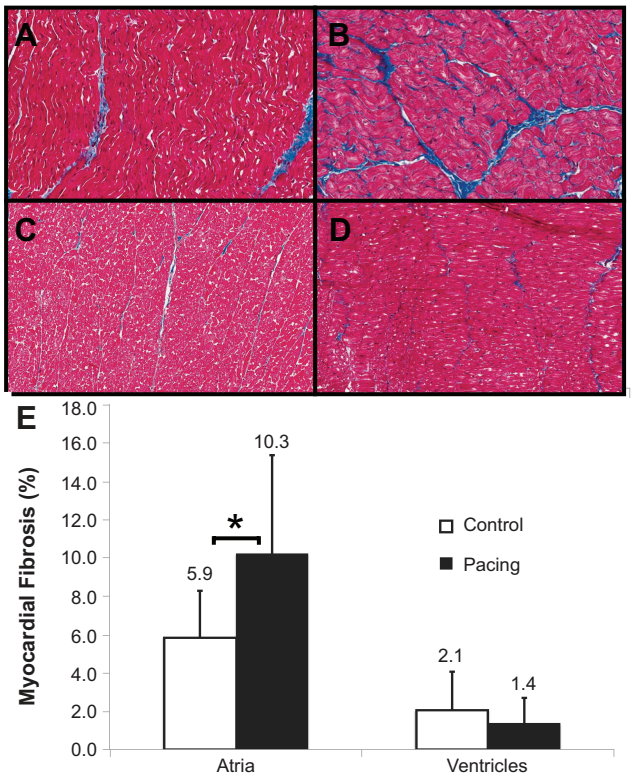

Fig. 5. Fibrosis in goats at baseline and after 6 mo of AF. *A*: LA sample from a control goat (4.8% fibrosis). *B*: LA sample from a 6-mo AF goat (10.1% fibrosis). *C*: LV sample from a control goat (0.8% fibrosis). *D*: LV sample from a 6-mo AF goat (1.4% fibrosis). *E*: atrial fibrosis levels increased, whereas there was no significant change in ventricular fibrosis levels. Values above bars indicate SDs. *$P <$ 0.01.

model is a poor choice for RAP studies lasting several months in duration.

Dogs proved to be the easiest species to work with, provided the highest MRI image quality, and developed sustained AF. Dog models of RAP-induced AF are widely published and are an established model of AF. The time to develop sustained AF in dogs was not statistically significantly longer than in goats, but dogs proved to be much more variable than goats. Previous chronic AF dog models have demonstrated that without medication, the ventricular response rate is fast (>220 beats/min) and that heart failure develops unless AV nodal ablation or pharmaceutical interventions are used (4, 23, 35). Rapid ventricular pacing induces congestive heart failure in dogs when pacing rates are 220–260 beats/min (10, 28). In the present study, dogs developed significant heart failure even when the ventricular

Table 2. *RAP-induced AF model characteristics by species*

	Pig	Dog	Goat
Ease of handling animals	−	+	0
Development of sustained AF	−	0	+
Heart failure burden	−	−	+
MRI imaging	0	+	−
Transmittable diseases	+	+	−
Publication history	−	+	0

RAP, rapid atrial pacing; −, relative disadvantage of the model; 0, neither advantageous nor disadvantageous; +, relative advantage of the model.

Table 3. *RAP pig studies with chronic AF lasting 3 wk or more*

Reference	Species	AF Duration	Time to Sustained AF	Notes
Bauer et al. (6)	Pig	3 wk	5 ± 0.7 days	EF dropped from 70 ± 2% at baseline to 28 ± 2% at 3 wk. HR increased from 115 ± 17 to 274 ± 5 beats/min in AF and severe congestive heart failure developed. There was a 1.5- to 4-fold increase in atrial fibrosis and 1.5- to 4-fold increase in ventricular fibrosis.
Lin et al. (18)	Pig	3–4 wk	25 ± 3 days	Animals were given digoxin (0.25 mg daily, oral). Baseline LV EF was 71 ± 12% and AF LV EF was 68 ± 10%. There was 4- to 5-fold increase in extracellular matrix content.
Lai et al. (17)	Pig	6 wk	50% AF after 4 wk	
Lin et al. (19)	Pig	6 wk	AF (minimum of 24 h) in 20 of 22 pigs	There was no observed interstitial or patchy fibrosis.

LV, left ventricular; EF, ejection fraction.

response rate was controlled (<180 beats/min) to a sufficient extent such that ventricular tachycardia-induced heart failure should not have developed (Table 1). Since the rate in this study was controlled so that the ventricular heart rate was <180 beats/min, the development of tachycardia-induced heart failure should have been minimized. Whether heart failure developed due to the rapid ventricular response rate or because of the irregularity of the induced ventricular rhythm was not determined in this study.

Investigators have developed models of RAP-induced AF with full AV nodal ablation and slower (80–100 beats/min) ventricular pacing to separate the effects of irregular, rapid ventricular rate and AF. A recent study (4) showed that 3 mo of RAP-induced AF in dogs caused an increase in both atrial and ventricular fibrosis, whereas RAP-induced AF in dogs with AV nodal ablation and 80 beats/min ventricular pacing caused a lesser degree of atrial fibrosis and did not increase ventricular fibrosis. In this study, pharmacological slowing of AV nodal conduction was not sufficient to halt the development of AF-induced heart failure in the dog model. The statistically significant increase in ventricular fibrosis in the canine model in this study was likely due to the development of heart failure.

Goats provided a predictable, sustained AF model that did not develop significant ventricular dysfunction as measured by LV EF. The cyclical rumen contractions during MRI imaging made atrial wall imaging difficult. An additional concern with goats is that they can be carriers of *Coxiella bunetii*, the bacteria that causes Q-fever. Conducting procedures in hospital settings such as in the EP laboratory or in clinical scanners require stringent additional decontamination and containment measures to prevent the infection of individuals in direct and indirect animal contact (e.g., fomite or aerosolization), particularly in patients with compromised immune systems.

While there are dozens of published studies with RAP-induced AF with 2–8 wk of pacing, a limited number of recent studies have conducted RAP-induced AF studies for 3–6 mo (Table 4). The limited data available from chronic AF studies

Table 4. *RAP goat and dog studies with chronic AF lasting 3 mo or more*

Reference	Species	AF Duration	Time to Sustained AF	Notes
Verheule et al. (27)	Goat	6 mo	100% by 4 mo	There was at least a 4-fold increase in myocyte-to-myocyte distance in atria.
Eckstein et al. (14)	Goat	6 mo	100% by 10 wk	Atrial intermyocyte distances had a 3- to 4-fold increase versus baseline.
Ausma (3)	Goat	9–23 wk	N/A	There was an increase in atrial myolysis and myocyte size but no detectable increase in the atrial extracellular matrix.
Verheule et al. (26)	Goat	6 mo	N/A	There was a 4- to 5-fold increase in distance between atrial myocytes.
Eckstein et al. (15)	Goat	6 mo	N/A	There was a 3- to 4-fold increase in distance between atrial myocytes.
Ausma et al. (2)	Goat	4 mo	N/A	There was a 2-fold increase in extracellular matrix content per atrial myocyte.
Avitall et al. (4)	Dog	3 mo	RAP of 12 ± 4 days	RAP baseline LV EF = 57 ± 5.4%; 3-mo LV EF = 30 ± 10%
			RAP with AVN ablation of 30 ± 13 days	RAP with AVN ablation baseline LV EF = 55 ± 5% and was unchanged at 3 mo. RAP = 3- to 4-fold increase in atrial fibrosis; RAP with AVN ablation: 2- to 3-fold increase in atrial fibrosis.
Zhang et al. (35)	Dog	6 mo	N/A	AVN dysfunction was observed during AF.
Avitall et al. (5)	Dog	202 ± 80 days	45 ± 43 days	Normal dogs HR = 113 ± 19 beats/min; AF dogs HR = 176 ± 41 beats/min. Normal dogs LV EF = 61 ± 3%; AF dogs LV EF = 60 ± 8%.
Chiu et al. (9)	Dog	4–5 mo	118 ± 24 days	There was a 2-fold increase in atrial extracellular collagen matrix surface area fraction.
Wu et al. (32)	Dog	5–6 mo	139 ± 84 days	Animals were given 0.125–0.250 mg digoxin daily. Atrial fibrosis was not quantified, but subjectively only a mild increase in fibrosis was observed.

N/A, not available; AVN, atrioventricular node.

of >3 mo of AF have demonstrated that whereas electrical remodeling occurs in hours to days, structural remodeling occurs over weeks to months. Recent studies (14, 15, 26, 27) have shown that important conduction changes and structural remodeling occur as AF persists from a few weeks to several months in duration. Eckstein et al. (14) studied the time course of structural and electrophysiologic remodeling in goats at baseline and after 3 wk and 6 mo of RAP. They found that the atrial extracellular matrix increased from baseline by 27% at 3 wk and by 280% at 6 mo. Other changes, such as a myocyte dimension increase and endoepicardial dyssynchrony, were progressive with time as well (15, 26). While short-term electrical remodeling, such as the atrial effective refractory period and action potential duration, return to normal after the restoration of sinus rhythm, Ausma et al. (2) demonstrated that increased the AF inducibility and extracellular matrix remain, even after a period of several months after chronic AF. The establishment of long-term (>6 mo) models of AF will answer the question of whether structural remodeling continues to occur long after sustained AF is established. Given the high incidence of AF recurrence in patients with longstanding persistent AF, animal models with chronic AF of durations >2–8 wk may be important in revealing the causes of AF recurrence in these patients.

Limitations of the present study. All animals used in this study were juvenile animals purchased from approved sources for research purposes. The effect of age on AF inducibility or development of myocardial fibrosis was not evaluated in this study but may be of critical importance in the patient population.

This study was limited to RAP-induced AF models. While some patients may develop AF as a result of rapid ectopic foci (such as pulmonary vein firing), other mechanisms of AF onset and maintenance, such as congestive heart failure, autonomic nervous system activity, hypertension, and chronic atrial stretch, were not investigated in this study.

Conclusions. RAP in the pig model did not consistently lead to sustained AF. Both the goat and dog models of RAP-induced AF have clinical relevance to patients with chronic AF. Some patients are asymptomatic and have normal ventricular heart rates or heart rates well controlled with β-blockers. Other patients with AF are not well rate controlled, and heart failure is a common comorbidity with AF patients. Depending on the aims of the study, either the dog or goat model of AF may be appropriate.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: D.J.D., R.R., K.H., R.M., L.N., A.O., C.J.D., and N.F.M. conception and design of research; D.J.D., R.R., K.H., E.G.K., N.A., L.N., A.O., and C.J.D. performed experiments; D.J.D., R.R., E.G.K., N.A., and L.L. analyzed data; D.J.D., N.A., R.M., L.N., and N.F.M. interpreted results of experiments; D.J.D. and N.A. prepared figures; D.J.D. drafted manuscript; D.J.D., N.A., L.L., R.M., and L.N. edited and revised manuscript; D.J.D., R.R., K.H., E.G.K., N.A., L.L., R.M., L.N., A.O., C.J.D., and N.F.M. approved final version of manuscript.

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