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Validation of a New Species for Studying Postoperative Atrial Fibrillation: Swine Sterile Pericarditis Model

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ORIGINAL ARTICLE

Validation of a new species for studying postoperative atrial fibrillation: Swine sterile pericarditis model

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Abstract

Background: The canine sterile pericarditis model associated with atrial inflammation is an experimental counterpart of postoperative atrial fibrillation (POAF). However, the use of canines for research is restricted by ethics committees in many countries, and social acceptance is declining.

Objective: To validate the feasibility of the swine sterile pericarditis model as an experimental counterpart to study POAF.

Methods: Seven domestic pigs (35–60 kg) underwent initial pericarditis surgery. On two or more postoperative days in the closed-chest state, we performed electrophysiological measurements of pacing threshold and atrial effective refractory period (AERP) while pacing from the right atrial appendage (RAA) and the posterior left atrium (PLA). The inducibility of POAF (>5 min) by burst pacing was determined in both the conscious and anesthetized closed-chest state. These data were compared to previously published canine sterile pericarditis data for validation.

Results: The pacing threshold increased from day 1 to day 3 (2 ± 0.1 to 3.3 ± 0.6 mA in the RAA, 2.5 ± 0.1 to 4.8 ± 0.2 mA in the PLA). Also, the AERP increased from day 1 to day 3 (118 ± 8 to 157 ± 16 ms in the RAA; 98 ± 4 to 124 ± 2 ms in the PLA, both $p < .05$). Induction of sustained POAF occurred in 43% (POAF CL range 74–124 ms). All electrophysiologic data from the swine model were consistent with the canine model with respect to (1) the range of both pacing threshold and AERP; (2) the progressive increase in threshold and AERP over time; (3) a 40%–50% incidence of POAF.

Conclusion: A newly developed swine sterile pericarditis model demonstrated electrophysiologic properties consistent with the canine model and patients after open heart surgery.

KEYWORDS
animal model, postoperative atrial fibrillation, sterile pericarditis

Abbreviations: AEGs, atrial electrograms; AERP, atrial effective refractory period; AF, atrial fibrillation; BB, Bachmann's bundle; CL, cycle length; IVC, inferior vena cava; LAA, left atrial appendage; PLA, posterior left atrium; POAF, postoperative atrial fibrillation; PV, pulmonary vein; RAA, right atrial appendage; RV, right ventricle; SVC, superior vena cava.

1 | INTRODUCTION

Postoperative atrial fibrillation (POAF) is the most common complication arising following open heart surgery, occurring in 30%–50% of patients with no prior history of AF.[1] It is associated with increased in-hospital and 6-month mortality, as well as in-hospital morbidity, including hemodynamic compromise, heart failure, and stroke.[2] POAF is no longer considered a transient one-time event as it is associated with an increased long-term vulnerability to the development of AF.[3,4] A recent clinical study showed that a longer duration of POAF is associated with worsened long-term survival.[5–7]

The canine sterile pericarditis model associated with atrial inflammation is an experimental counterpart of POAF. Using that model, we demonstrated that epicardial inflammation and its proliferation occurring in the atria produces a loss of epicardial myocytes and an altered distribution of connexins 40 and 43.[8] These changes are associated with non-uniform slowing of conduction, thus creating the vulnerable substrates for the initiation and maintenance of POAF. In addition, the inducibility of POAF in the canine model is consistent with the time course of atrial arrhythmias in patients after open heart surgery, both peaking 2–4 days after surgery.[9] However, the use of canines for research is restricted by ethics committees in many countries, and social acceptance is declining. Recently, the swine has been increasingly used for cardiac research because it has similar physical and electrophysiological properties to humans, and is socially more accepted.[10,11] Although a recent study reported a model of sterile pericarditis-induced atrial myopathy in Aachen minipigs, the study failed to induce POAF during postoperative period (within 5 days) after open heart surgery.[12] The purpose of this study is to validate the feasibility of the swine sterile pericarditis model as an experimental counterpart to study POAF. To do this, we compared the electrophysiologic data between the swine pericarditis model and previously published canine sterile pericarditis model for validation.[13]

2 | METHODS

Animal experimental protocols were approved by the Case Western Reserve University Institutional Animal Care and Use Committee (IACUC). All studies were performed by the guidelines specified by our IACUC, Department of Agriculture Animal Welfare Act, Public Health Service Policy on Humane Care and Use of Laboratory Animals, and Association for Assessment and Accreditation of Laboratory Animal Care International.

2.1 | The creation of the swine sterile pericarditis model

Sterile pericarditis was created in seven domestic pigs weighing 35–60 kg (age 3–5 months). Under general anesthesia, the pigs underwent a right thoracotomy between the 4th and 5th rib in the 4th intercostal space. The heart was exposed and cradled in the pericardium using standard surgical techniques. The temporary bipolar pacing wire (Streamline 6495, Medtronic, MN) was secured into the posterior left atrium (PLA, between the right inferior pulmonary vein and coronary sinus, Figure 1). Pair of stainless steel wire electrodes coated with EDP polymer except for the tip were sutured to the right atrial appendage (RAA). Also, another electrode pair was sutured onto the right ventricle for monitoring during the conscious closed-chest state study. All three electrodes were brought out through the chest wall, and exteriorized posteriorly in the middle of the neck for use in pacing and recording. Then, the atrial surfaces were dusted with sterile talcum powder, and a double layer of gauze was placed on both the right and left atrial free wall. These steps create the irritant for the level of pericarditis required to have an effective arrhythmia model. The pericardiotomy was repaired, and the chest was closed in a standard fashion. Finally, antibiotics and analgesic agents were administered, and the pigs were allowed to recover.

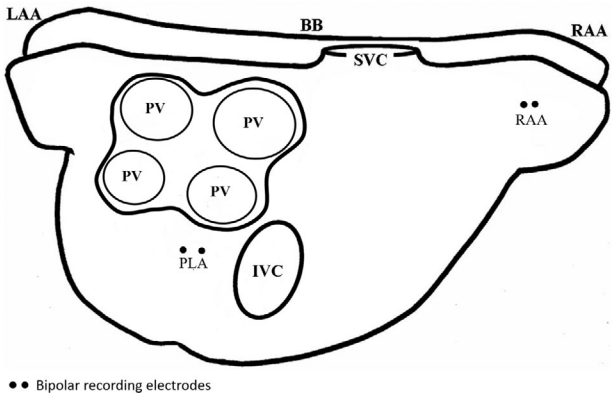

FIGURE 1 Atrial bipolar electrode locations. Shown are the locations of the two bipolar atrial electrodes (black dots) for pacing and recording on the epicardial surface of the atrium. BB, Bachmann's bundle; IVC, inferior vena cava; LAA, left atrial appendage; PLA, posterior left atrium; PV, pulmonary vein; RAA, right atrial appendage; SVC, superior vena cava.

2.2 | Electrophysiology study protocol

In the conscious or anesthetized close-chest states, all pigs underwent basic electrophysiologic studies on two or more of postoperative days 1, 2, 3, or 4. The basic electrophysiologic study was performed as follows: baseline measurements were made to determine the stimulus threshold for atrial capture and atrial effective refractory period (AERP) at each electrode site (RAA and PLA). AERPs were determined at twice the capture threshold. All parameters were measured at pacing CLs of 400, 300, and 200 ms (Figure 2A).

2.3 | POAF induction protocol

POAF induction was attempted using rapid atrial pacing for 1–5 s performed from each atrial electrode site beginning at a cycle length (CL)

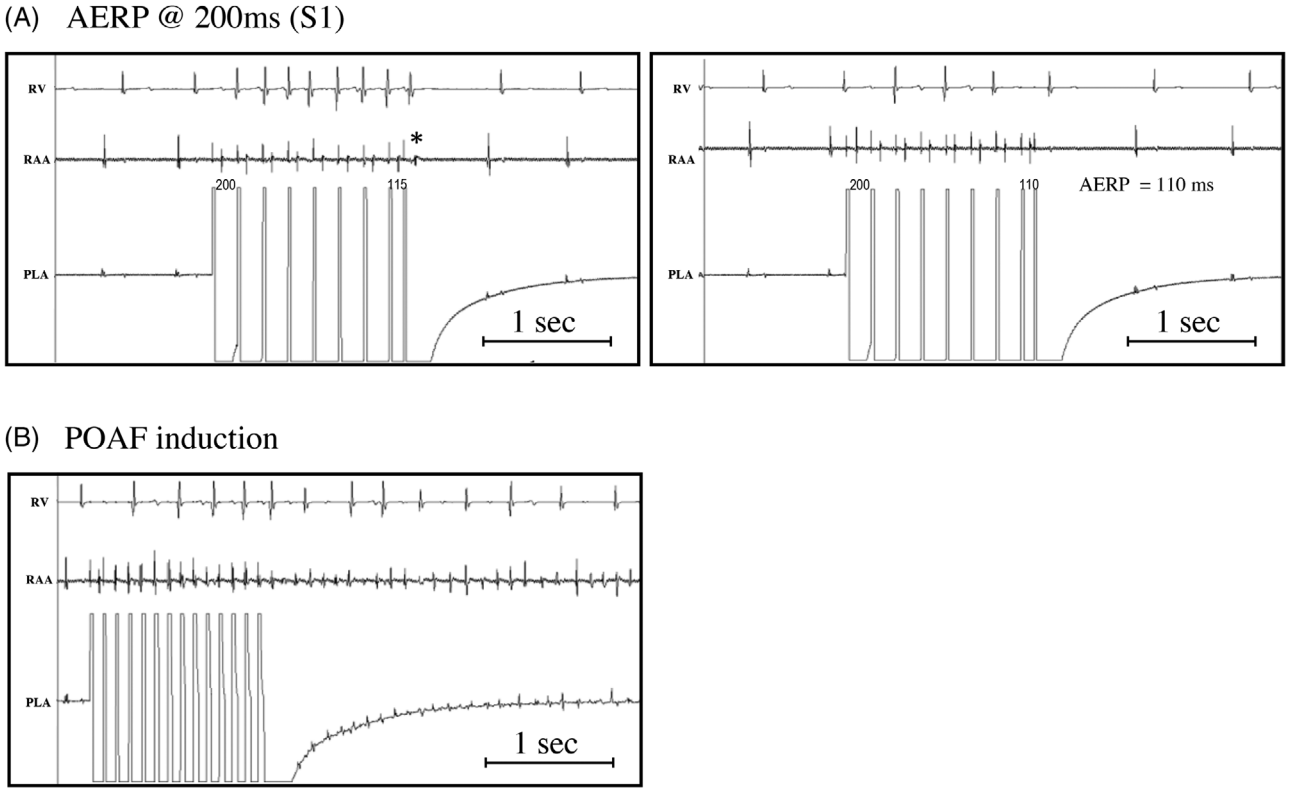

FIGURE 2 Simultaneous recordings from selected atrial sites (RAA and PLA) during the conscious closed-chest state study in the swine sterile pericarditis model (pig #3). (Panel A): A representative example of the AERP study with atrial capture (*, S2 = 115 ms) and failure of atrial capture (S2 = 110 ms) following an eight-beat atrial drive train (S1) at CL of 200 ms using stimuli of twice threshold. The AERP was defined as the longest S1-S2 interval that failed to capture the atria (AERP = 110 ms). (Panel B): POAF induction was attempted using rapid atrial pacing for 1.3 s performed from the PLA site at a CL of 102 ms. AERP, atrial effective refractor period; CL, cycle length; PLA, posterior left atrium; RAA, right atrial appendage; RV, right ventricle.

of 120 ms, and decrementing by 2–5 ms until loss of capture or POAF is achieved (Figure 2B). All pacing was performed with a pulse width of 1.8 ms, and a stimulus strength sufficient to obtain atrial capture. After POAF is induced, its duration is characterized. Sustained POAF was defined as more than 5 min. In both the conscious and anesthetized close-chest state, both electrophysiological study and POAF induction protocols for all study components were performed with a Bloom DTU stimulator (Bloom Electrophysiology, Denver, CO). Both the induction of and ensuing sustained POAF (>5 min) was recorded using Bard LabSystem PRO (Bard Electrophysiology, Lowell, MA), to record atrial electrograms (AEGs) from the bipolar electrodes placed at the RAA, PLA, and right ventricle.

2.4 | Statistical analysis

Data are presented as the mean ± SD. Minitab (Minitab Inc., State College, PA) was used for statistical analyses. The student's paired t-test (normally distributed variables) or a Wilcoxon signed rank test (non-normally distributed variables) was used to compare differences in the threshold and AERP in PLA and RAA of postoperative days. Normality was assessed using Jarque-Bera test. Also, the student's t-test was used to compare differences between pigs and dogs in the AERP in PLA and RAA of postoperative days. A value of $p \leq .05$ was considered statistically significant.

3 | RESULTS

3.1 | Electrophysiology properties (Threshold and AERP) on postoperative days 1–3

In the conscious and anesthetized close-chest states, the pacing threshold for capture was increased from postoperative day 1 to day 3 (Figure 3A). Mean RAA and PLA atrial threshold from all pacing CLs on postoperative day 1 versus day 3 were as follows: 2 ± 0.1 to 3.3 ± 0.6 mA in the RAA, $p \leq .05$; 2.5 ± 0.1 to 4.8 ± 0.2 mA in the PLA. Also, the AERP at the twice-threshold was significantly increased in both atria from postoperative day 1 to day 3 (118 ± 8 to 157 ± 16 ms in the RAA; 98 ± 4 to 124 ± 2 ms in the PLA, both $p \leq .05$, Figure 3B). Table 1 shows the summary data (pig vs. dog) of AERP from RAA and PLA in each pacing CL (400, 300, and 200 ms) on postoperative days 1–3. Although the AERP at pacing CLs of 200 ms in the swine model was significantly shorter than the canine model on postoperative day 1,

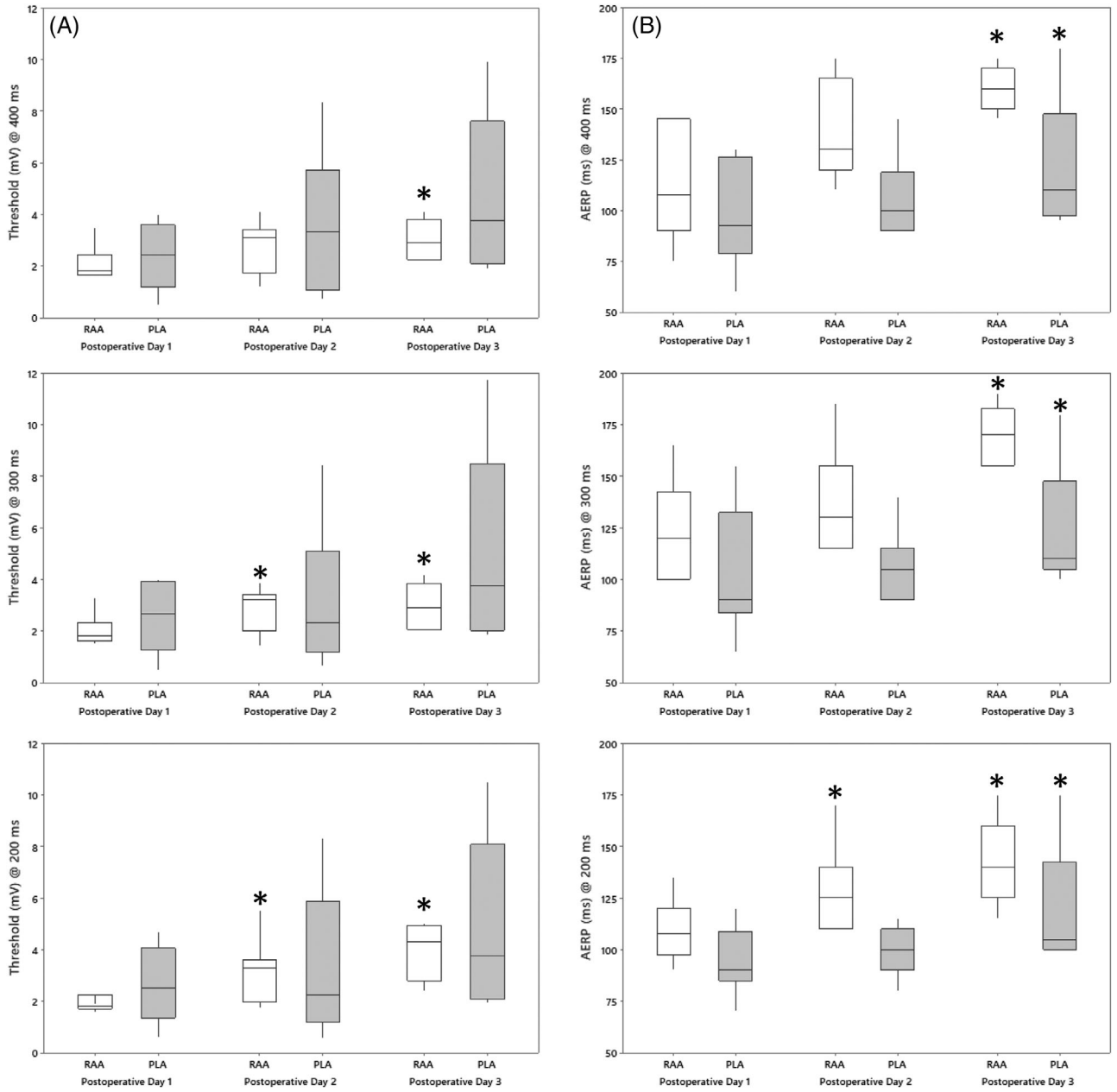

FIGURE 3 Box plots illustrating the range of mean pacing threshold for capture (A) and mean AERP (B) of all pigs combined for PLA and RAA during postoperative days 1–3. The box represents the 25th to the 75th percentile, the horizontal line in the box represents the median, and the vertical line represents the minimum and maximum values. *indicates statistical significance ($p \leq .05$) compared to postoperative day 1. See text for Discussion.

most AERP from the swine model was consistent with the canine model on postoperative days.

3.2 | Inducibility of sustained POAF in the closed-chest studies

POAF induction was attempted on days 1–4 for 2 pigs, on days 1–3 for 3 pigs, and on days 1–2 for 2 pigs, for a total of 21 days of the study. On postoperative day 1, two pigs were not able to perform the POAF induction study in the conscious closed-chest state due to the pig condition. Induction of sustained POAF occurred in 43% (3/7 pigs, POAF CL range 74–142 ms). Attempting to induce POAF was performed for approximately 30 min depending on the pig's disposition. One of the sustained POAF episodes spontaneously converted to atrial flutter, which is common after open heart surgery.[14] Each episode is summarized in Table 2.

TABLE 1 Atrial ERP (AERP).

Pacing site	Pacing CL (ms) at 2× threshold	Postoperative day 1		Postoperative day 2		Postoperative day 3	
		Dog ($n = 6$)	Pig ($n = 6$)	Dog ($n = 6$)	Pig ($n = 7$)	Dog ($n = 6$)	Pig ($n = 5$)
RAA	400	136 ± 20	113 ± 28	145 ± 28	140 ± 25	179 ± 32	160 ± 11
	300	138 ± 21	127 ± 34	149 ± 20	146 ± 31	160 ± 20	172 ± 18
	200	131 ± 12	113 ± 23*	138 ± 13	135 ± 24	141 ± 18	140 ± 5
PLA	400	127 ± 18	98 ± 26	132 ± 20	106 ± 21	151 ± 29	125 ± 38
	300	120 ± 20	103 ± 32	130 ± 23	107 ± 17	148 ± 29	126 ± 36
	200	121 ± 11	94 ± 17*	121 ± 17	99 ± 12*	144 ± 28	123 ± 35

Note: For AERP, *t*-test (pig vs. dog) was used.
Abbreviations: AERP, atrial effective refractory period; PLA, posterior left atrium; RAA, right atrial appendage.
*indicates statistical significance ($p < 0.05$).

TABLE 2 Postoperative AF episodes.

Pig #	Postoperative day	State	Rhythm	Time at longest episode	CL range
1	1	Conscious closed-chest	No induction attempt		
	2	Conscious closed-chest	POAF	42 s	102–120 ms
	3	Anesthetized closed chest	POAF	>10 min	118–124 ms
2	1	Conscious closed-chest	No induction attempt		
	2	Conscious closed-chest	POAF	6 s	116– 142 ms
	3	Conscious closed-chest	POAF	20 s	108–124 ms
	4	Anesthetized closed chest	POAF	11 s	116–154 ms
3	1	Conscious closed-chest	POAF	>10 min	74–90 ms
	2	Conscious closed-chest	POAF	8 s	94–126 ms
	3	Conscious closed-chest	POAF	8 s	88–128 ms
	4	Anesthetized closed chest	POAF	16 s	116–176 ms
4	1	Conscious closed-chest	POAF	52 s	66–134 ms
	2	Anesthetized closed chest	POAF to AFL	>10 min	83–142 ms à 162 ms
5	1	Conscious closed-chest	POAF	1 s	88–100 ms
	2	Conscious closed-chest	POAF	5 s	120–134 ms
	3	Anesthetized closed chest	POAF	2 s	90–134 ms
6	1	Conscious closed-chest	POAF	40 s	86–140 ms
	2	Anesthetized closed chest	POAF	21 s	114–138 ms
7	1	Conscious closed-chest	POAF	32 s	82–120 ms
	2	Conscious closed-chest	POAF	36 s	78–100 ms
	3	Anesthetized closed chest	POAF	8 s	116–184 ms

Abbreviations: AFL, atrial flutter; CL, cycle length; POAF, postoperative atrial fibrillation.

4 | DISCUSSION

Seven domestic pigs underwent surgery for the creation of sterile pericarditis. We performed all electrophysiological studies and POAF induction in the closed-chest state during postoperative days, the same environment as patients after open heart surgery. In the conscious and/or anesthetized closed-chest states on postoperative days 1, 2, 3, and/or 4, we demonstrated the progressive increase in pacing threshold for capture and AERP over time. The induction of sustained POAF occurred in 43%, consistent with prior observations in the canine sterile pericarditis model and patients with POAF after surgery.[1,15] Also, one of the sustained POAF episodes converted to atrial flutter.

4.1 | Swine versus canine sterile pericarditis model for studying POAF

A canine sterile pericarditis model has been used to understand the mechanism of postoperative arrhythmias such as POAF or atrial flutter for onset, prevention, maintenance, and treatment.[8,13,15–20] Pericarditis is major contributor to the etiology of postoperative arrhythmias by creating an atrial substrate vulnerable to atrial arrhythmias.[8,21–23] In the canine sterile pericarditis model, inflammation of the pericardium and myocardium is created by placing gauze dusted with talcum powder on the atrial epicardium, and our group has shown that it alters the myocyte architecture and gap junctions, which lead to changes in the electrophysiological properties such as AERP and conduction velocity.[8] We are unaware of any other animal models of POAF, which are an experimental counterpart to pericarditis-related POAF following open heart surgery. POAF is usually transient or self-limiting, unlike other forms of AF, with a return to sinus rhythm once the atrial substrate, that is, postoperative pericarditis, resolves. The progressive increases in pacing thresholds and AERP over postoperative periods in the canine model are consistent with prior observations in patients with POAF after surgery.[24–26] In comparison with the swine sterile pericarditis model, all electrophysiologic data from the swine model were consistent with the canine sterile pericarditis model[9,13,15,16] with respect to (1) the range of both pacing threshold and AERP; (2) the progressive increase in threshold and AERP over time; (3) a 40%–50% incidence of POAF. In addition, the swine sterile pericarditis study can be performed in the conscious closed-chest state on postoperative days.

A recent study showed a model of sterile pericarditis-induced atrial myopathy in Aachen minipigs, suggesting a model of structural remodeling in AF.[12] The study demonstrated that atrial fibrosis resulting from the inflammation of the pericardium and myocardium preceded the induction of AF. In comparison with our study, the progressive increases in pacing thresholds over time are consistent. However, the study failed to induce POAF during postoperative period (within 5 days). The major differences compared to this study are weight (mini pigs [~20 kg] vs. farm pigs [~60 kg]) and POAF induction protocol (pacing at 2× threshold for 20 sec vs. pacing at more than 2× threshold for up to 5 sec). Perhaps the latter difference is most important because (1) pacing with a large stimulus strength is usually necessary, as the stimulus threshold for capture increases when pacing CLs decrease[27]; (2) pacing duration of 20 sec could initiate reentrant circuits then terminate them due to continuous pacing.

4.2 | Clinical implication

Although POAF in the swine sterile pericarditis is not spontaneous, it has several clinical implications. Given the wide spectrum of etiologies and disease processes associated with POAF, a reproducible swine sterile pericarditis model is essential to target the inflammation of the pericardium and myocardium that underline the development of the POAF. In addition, it can be used to identify the inflammation-related mechanisms of POAF for its onset, maintenance, treatment, and prevention. A swine heart, which is similar in size and physical and electrophysiological properties to the human heart, may be useful for developing medical equipment and advanced technologies in the clinical setting for electrophysiology procedures. Therefore, the more socially accepted swine sterile pericarditis model may potentially be used to model clinically equivalent postoperative arrhythmias in humans.

4.3 | Limitations

In addition to PLA and RAA, the canine sterile pericarditis model has an electrode site at Bachmann's bundle (BB) for pacing and recording. The difficulty in accessing BB during the initial surgery to create the swine sterile pericarditis did not allow for suturing the temporary bipolar pacing wire for recording and pacing, which may limit the options for POAF induction. Also, we did not record ECG limb leads during the conscious closed-chest state due to the difficulty of keeping ECG cable connected to a minimally restrained pig. However, we recorded from the right ventricular site for monitoring. Finally, although the swine sterile pericarditis model was developed as an experimental counterpart of POAF after open heart surgery, the mechanism that sustains POAF in patients may have more than one mechanism responsible for its maintenance due to various comorbidities, different surgery types, and complication during surgery in patients.[28]

5 | CONCLUSION

A newly developed swine sterile pericarditis model demonstrated electrophysiologic properties consistent with the canine model. The induction of sustained POAF occurred in 43%, consistent with prior observations in the canine model and patients with POAF after surgery. Therefore, the swine model is feasible as an experimental counterpart to study POAF.

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CONFLICTS OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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