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Application of Insertable Cardiac Monitor in Establishing a Dog Model of Atrial Fibrillation by High-Frequency Right Atrial Pacing

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Background: On the base of traditional modeling with high-frequency atrial pacing, insertable cardiac monitor is innovative-ly used to track the incidence of atrial fibrillation (AF), to observe the efficiency and safety of establishment in AF model.





Material/Methods: Twelve adult beagle dogs were randomly divided into a blank control group and an AF model group. The thinnest available bipolar solid electrode lead-3830 was implanted in AF group, connected to AF pacemaker to establish a high-frequency atrial pacing model by AOO pacing mode, and the occurrence of AF was tracked in real time by an insertable cardiac monitor Reveal LINQ. The areas of the left and the right atrium were measured by echocardiography. In addition, the morphology of left atrial tissues was observed using light and electron microscopes.

Results: The insertable cardiac monitor Reveal LINQ sensitively, conveniently, accurately, efficiently, and dynamically recorded the AF load in AF group. After the successfully establishment of the AF mode, the area of the left atrium and right atrium were significantly enlarged compared with that before modeling by echocardiography. Furthermore, the area of the left atrium and right atrium in the AF group were larger than that in the control group. The morphological observation of the left atrium tissues in both groups prompted the reconstruction of the atrial structure in dogs in the AF group.

Conclusions: The application of insertable cardiac monitor Reveal LINQ improves the efficiency of monitoring the AF load, with high sensitivity, convenience, and accuracy.

MeSH Keywords: **Animal • Atrial Fibrillation • Insertable Cardiac Monitor • Models**

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Background

Atrial fibrillation (AF) is the most common arrhythmia in clinical settings. The absence of effective atrial systolic and diastolic functions leads to a poor quality of life, secondary heart failure, ischemic stroke, and sudden arrhythmic death [1]. This disease has a high morbidity and mortality [2], and it has become a chronic non-infectious cardiovascular epidemic posing a serious threat to human health. With the advances in basic and clinical research, the diagnosis and treatment of AF has been significantly improved, and its mechanism has gradually been elucidated [3]. However, the treatment of AF is still not optimistic. Therefore, studies on the mechanism of and the development of new therapies for AF are urgent [4]. The establishment of a stable AF animal model is of great significance to more comprehensive investigation of the mechanism of AF.

In this study, an animal model of AF was established using rapid atrial pacing. For the first time, using the SelectSecure system, a rapid atrial pacing system was established by the smallest bipolar solid electrode lead 3830, which is only 4.1Fr in diameter [5]. Meanwhile, Reveal LINQ, an insertable cardiac monitor with “precision”, “fine”, and “delicate” modes, was used to detect and record the occurrence of AF, as well as to improve the efficiency of establishing the AF model by high-frequency pacing.

Material and Methods

Experimental animals

A total number of 12 adult beagle dogs (weighing 12–16 kg), aged 7–12 months, male or female, were provided by the Experimental Animal Center, Kunming Medical University (Kunming Yunnan, China). The laboratory animal license number was the following: SYXK (Yunnan) K2015-0002. The experiment was examined and approved by the Animal Laboratory Ethics Review Committee of Kunming Medical University (Ethics Approval No. KMMU2018022, Approval Time: January 2016). The experiments were performed in accordance with the Guide for the Care and Use of Laboratory Animals issued by the National Institute of Health. Animals were randomly divided into a blank control group (Ctrl group, n=6) and an AF model group (AF group, n=6). Before the experiments, skin preparation was performed of all animals using an electric clip at both sides of the neck, bilateral inguinal regions, anterior part of chest, the L2–L3 regions of the waist, and the limbs.

Establishment of the dog model of rapid right atrial pacing

In the AF group, routine skin preparation was performed, after which they were placed in the lateral position on a catheterization

table. Then, they were given nasal cannula for a low-flow oxygen inhalation and were intravenously anesthetized with 3% pentobarbital sodium (30 mg/kg), in which the anesthetization was maintained by 3% pentobarbital sodium 2 mg/kg per hour. During the operation, the standard limb lead ECG, (I, II, III, aVR, aVL, and aVF) heart rate, blood pressure, oxygen saturation, and respiratory rate were continuously monitored. Under aseptic conditions, the right external jugular vein was punctured, a 100-cm long J-shaped guidewire was inserted to the inferior vena cava, and the Select Site™ sheath system (Medtronic Inc., Minneapolis, MN, USA) was assembled and inserted to the right atrium along the guidewire. Further, the guidewire was slowly removed, the sheath was flushed with heparin water. Next, the 3830 bipolar solid atrial pacing lead (Medtronic Inc., Minneapolis, MN, USA) was accurately inserted into the hemostatic valve and pushed to the black mark at the top of the sheath at which the rotated electrode was intended to be screwed into. Then, the 3830 rotated electrodes were screwed and positioned at the high right atrium to fix the sheath. After that, the electrode leads were slowly pushed until the spiral ring reached 2–3 cm beyond the catheter and contacted the atrial muscle wall. Subsequently, the electrode leads were rotated, 3–4 turns in a clockwise direction. X-ray fluoroscopy was employed to confirm the lead fixation, and the test pacemaker electrode parameters (threshold, pulse width, sensing, output, lead impedance, and battery status) were measured. When satisfactory parameters were achieved, the sheath tube was removed, and the lead was fixed. The electrode was then connected with the AF model pacemaker (Qinming, Shanxi, China), and the implantable high-frequency (90–810 beats/minute) AF model pacemaker was embedded in the anterolateral cervical pouch (Figure 1). After confirmation of normal vital signs, penicillin 800 000 U was injected for 3 days to prevent infection. The right atrial pacing system was not established in the control group.

Establishment of atrial pacing animal model

Postoperatively, the AF model was constructed. The high-frequency pacemaker was programmed to the AOO pacing mode by using a pacemaker program controller (Qinming, Shanxi, China), and the output and pulse width of the pacemaker were set to values 2-fold higher than the measured threshold. The basic stimulation frequency of the pacemaker was set at 90 times/minute. The basic conditions of the dogs were observed, including breathing, heart rate, diet, exercise, as well as the appearance of heart failure and other abnormal signs. The animals were considered to have the symptoms of heart failure if tachypnea, fast heart rate, poor appetite, cold limbs, vomiting and exhaustion appeared. According to the actual situation, continuous or intermittent high-frequency pacing of the right atrium was applied. The pacing stimulation frequency was gradually adjusted, with an increment step of 10–20 beats/minute. Every week, the standard ECG of the



Figure 1. Establishment of high-frequency right atrial pacing in dogs. (A) Puncture the right external jugular vein and insert the guide wire. (B) Implant the 3830 electrode wire through Select Site™ sheath system. (C) The parameters of pacemaker electrodes were measured by connecting detector across bridge line. (D) Pacing electrode parameters were examined during operation. (E) Pacemaker is connected to the pacemaker electrode. (F) The pacemaker was placed in the anterolateral cervical pouch. (G) Stitch the wound of pacemaker pocket. (H) Bandaging the incision of Pacemaker pouch. (I) The images suggest that the right atrial pacing system has been successfully established.

limb leads was depicted, combining with the data recorded by the insertable cardiac monitor Reveal LINQ (Medtronic Inc., Minneapolis, MN, USA). AF can occur without the need for programmed atrial stimulation after closing pacemaker function in AF model. If the ECG showed that the P wave was replaced by the wave with irregular size, shape, and time limit, as well as irregular ventricular rhythm, it prompted the appearance of

AF [6], of which the AF that persisted for longer than 15 minutes was defined as persistent AF.

Implantation of reveal LINQ tracker

Insertable cardiac monitor (ICM) is an implantable monitoring system for the detection and identification of unpredictable,

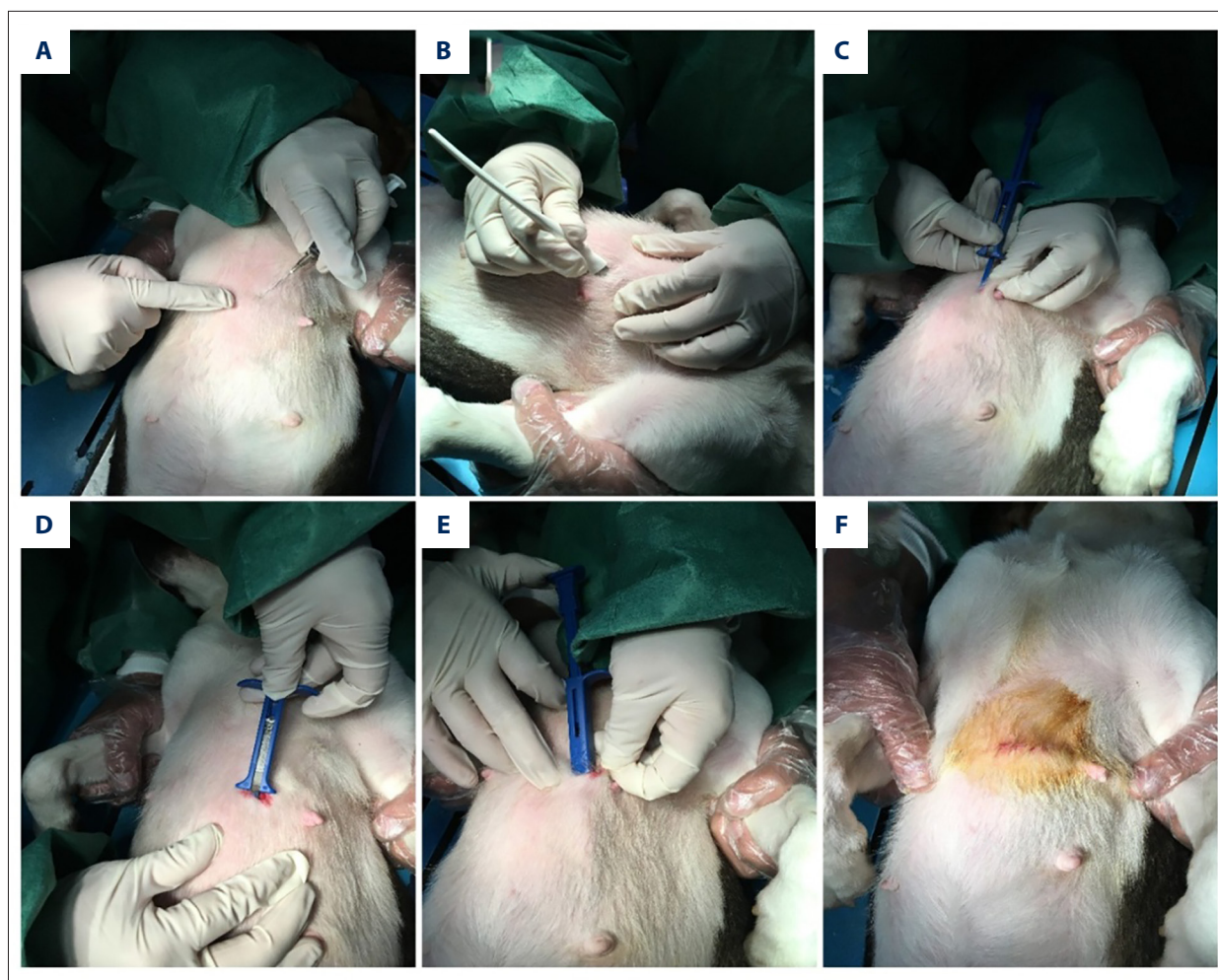


Figure 2. Implantation of Reveal LINQ. (A) The experimental dog was placed in the supine position on the operating table. The implantation site was located between the fourth and fifth ribs of the chest, 2 cm from the left margin of the median line. (B) A skin incision was made with a special scalpel. (C) The subcutaneous tissues were separated with a separating tool. (D) The subcutaneous tissues separated by the separating tool formed an implantation pathway. (E) The insertable cardiac monitor Reveal LINQ to be implanted was injected with matching injection tools. (F) Reveal LINQ was successfully established.

infrequent episodes of clearly prognostic arrhythmias, such as the cause of syncope, AF, and other arrhythmias. The Medtronic Reveal LINQ (Medtronic, Minneapolis, MN, USA) is a novel ICM. It is much smaller than its predecessor, only 7×45×4 mm in size, and adopts wireless telemetry remote monitoring technology and new AF recognition algorithm [7], Reveal LINQ ICM is an electrodeless wire device implanted subcutaneously in the chest. There are 2 electrodes on the device to continuously monitor a patient's subcutaneous ECG. Accurate algorithm can make Reveal LINQ record AF sensitively, accurately and efficiently, The ECG data and event report of dynamic monitoring were collected easily and safely by programmer.

The AF automatic algorithm of Reveal LINQ is mainly based on R-R interval and P-wave integral. Based on the previous

R-R interval recognition algorithm, Reveal LINQ adds the algorithm of AF based on P-wave integration, which can reduce the inappropriate recognition of AF. The algorithm is based on 2-minute ECG record, which is recognized as AF at the end of a 2-minute detection period, then the 2-minute ECG is stored. The automatic wireless transmission function of the Reveal LINQ automatically transmits the last 10 seconds of the longest AF episode every night. The patient can manually and wirelessly transmit all ECG event records. The reveal LINQ device can store 59 minutes of ECG data, which is convenient to collect and view ECG event information [7,8].

Reveal LINQ was implanted in the experimental dogs in the AF group. The dogs were placed in the supine position, and the front chest was routinely disinfected, paved with towels,

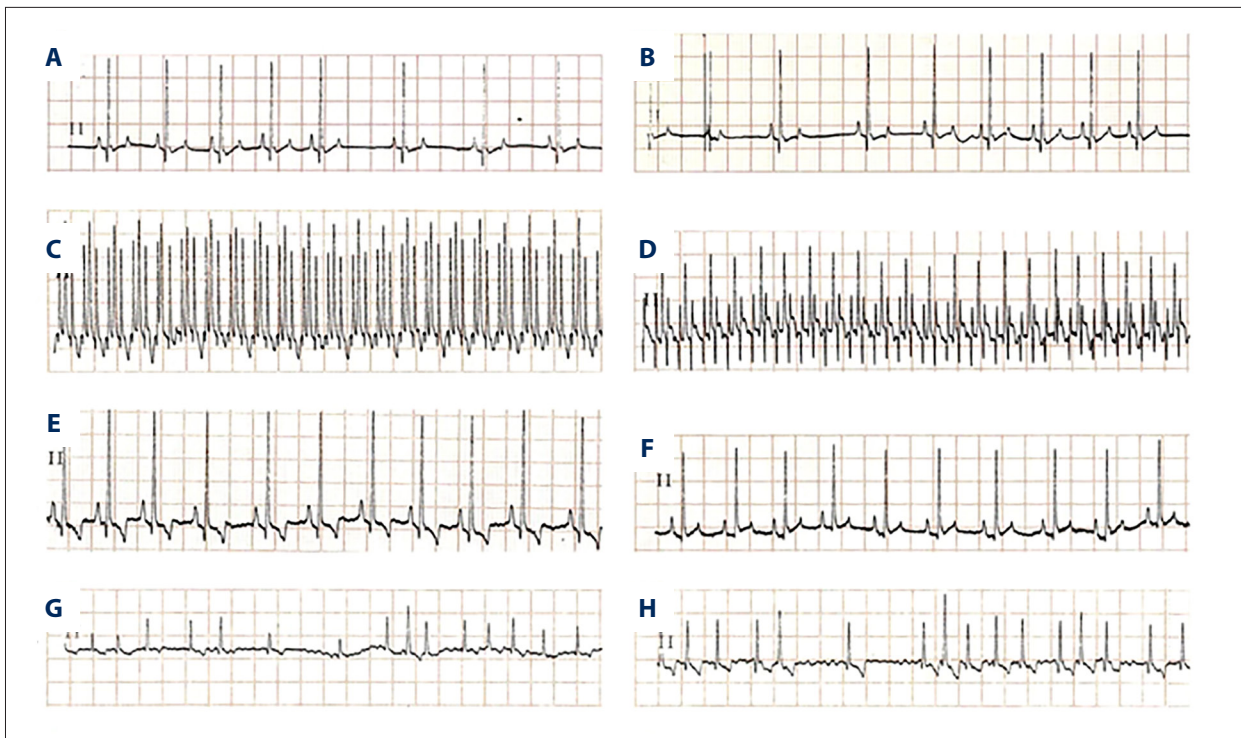


Figure 3. Electrocardiography (ECG) during and after the establishment of the atrial fibrillation (AF) model. (A, B) ECGs were performed before the operation of the experimental dogs, showing a sinus rhythm. (C, D) AF models were established by rapid atrial pacing. (E, F) In the establishment of the AF model, the atrial stimulation frequency of the pacemaker in the high-frequency AF model was 500 beats per minute. After closing the pacing function of the pacemaker, ECG showed a sinus rhythm, tachycardia and peaked P waves. (G, H) AF models were successfully established. The ECG showed that the P wave disappeared and was replaced by an irregular tremor wave with an irregular size, shape and time limit, and an irregular ventricular rhythm.

positioned between the fourth and fifth ribs of the chest, 2 cm at the left margin of the median line of the chest and 45 degrees at the angle of the median line of the chest. After successful positioning, local anesthesia with lidocaine was applied, the skin was incised with a special scalpel, and subcutaneous tissue was separated by a separating tool to form an implantation pathway. Finally, the ECG monitor was implanted with a matching insertion tool (Figure 2). All experimental dogs implanted with Reveal LINQ had no complications without the catheter intervention. The implantation process was simple and safe. The parameters of the post-operative programmed control were set, among which, the AT/AF detection was set to “AF only” to record the AF load [7].

Echocardiographic examination

All enrolled Beagle dogs were examined by echocardiography before the surgery using GE Vivid q color echocardiography (GE, USA) with a probe emission frequency of 2.5 MHz. The animals in the AF group underwent echocardiography after successful establishment of AF and before execution, respectively, and those in the control group underwent echocardiography

at the same time. The areas of the double atrium were measured on the apical 4 chamber view, where the parameters were measured within the 3–5 cardiac cycle, and the average values were adopted.

Execution of animals and collection of tissue specimens

The experimental dogs of the 2 groups were sacrificed, and the chest was opened layer by layer in the midline of the chest, the heart was taken out, and left atrial tissue specimens were collected for examination. The specimens subjected to morphological light microscopy were fixed with 10% formaldehyde to prepare paraffin sections. The ones subjected to morphometric electron microscopy were fixed with 2.5% glutaraldehyde during the section preparation.

Statistical analysis

Statistical analyses were performed using SPSS 19.00 software. Measurement data in accordance with normal distribution were expressed as mean±standard deviation, of which the data of paired design were analyzed using paired *t*-test.

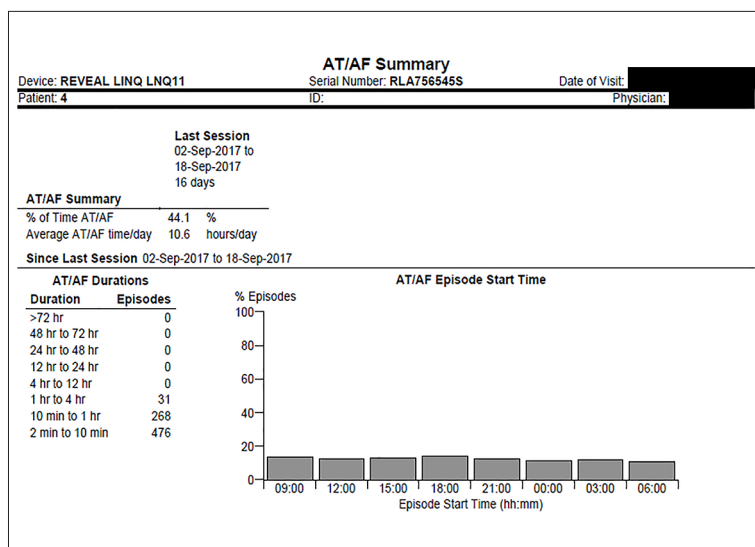


Figure 4. Atrial fibrillation (AF) events recorded by Reveal LINQ. When an experimental dog implanted with Reveal LINQ is programmed as AF only, during the monitoring period, the AF burden is 44.1%. The episode duration of AF indicates that it is paroxysmal AF.

Multiple comparisons of measurement data in accordance with normal distribution was performed using 2-independent sample *t*-test. A difference with $P < 0.05$ was considered statistically significant.

Results

General information

A total number of 12 dogs were enrolled in the study, 2 of which died during the modeling process, whereas the remaining 10 dogs completed the experiments. High-frequency pacemakers were successfully implanted, and the insertable cardiac monitor Reveal LINQ were also implanted in the animals in AF group. During the establishment of the AF model, 2 dogs suddenly died, in which was ventricular malignant arrhythmia found to have occurred based on the data obtained by the Reveal LINQ tracker. The 6 animals in the control group survived.

AF induction time and modeling success rate in AF modeling

A high-frequency AF pacemaker was successfully implanted in each of the animals in the AF group, which presented AF without programmed stimulation (Figure 3). The time to establish the AF was 10.63 ± 2.13 weeks. When the AF model was established successfully, the atrial stimulation frequency of the high-frequency AF pacemaker was 588.75 ± 11.26 beats/minute in the AOO pacing mode.

Reveal LINQ dynamically tracks AF burden

An ECG monitor Reveal LINQ was implanted to dynamically record the changes of the AF burden. The AF burden has been

correlated to the amount of time during which the heart is in AF. When the parameter was set to "AF only", the AT/AF record presented the duration of AF events, that is, the AF load was defined as the total onset time of AF when the Reveal LINQ tracker was programmed to be "AF only" [7]. The ECG data and event report of dynamic monitoring were collected easily, safely and non-invasively by programmer (Figure 4).

Comparison of areas of left atrium and right atrium in the dogs by echocardiography

A Vivid q color Doppler Ultrasonic Diagnostic Apparatus (GE, USA), with a probe emission frequency of 2.5 MHz, was used to examine the enrolled beagle dogs, in which the areas of the left atrium and right atrium at the end-systolic period were measured via the apical 4-chamber (Figure 5).

The paired *t*-test results showed that the area of the left atrium in the AF group was significantly higher (8.20 ± 0.83 cm² versus 3.80 ± 0.08 cm², $P < 0.05$) than the respective values before the establishment of the AF model. The area of the right atrium was also enlarged as compared with baseline values (4.52 ± 0.44 cm² versus 2.75 ± 0.96 cm², $P < 0.05$) (Table 1).

The paired *t*-test confirmed that the area of the left atrium in the AF group was significantly larger (8.20 ± 0.83 cm² versus 3.72 ± 0.15 cm², $P < 0.05$) than that in the control group; the area of the right atrium in the AF group was also greater than that in the control (4.52 ± 0.44 cm² versus 2.78 ± 0.18 cm², $P < 0.05$) after the AF model was successfully established (Table 2).

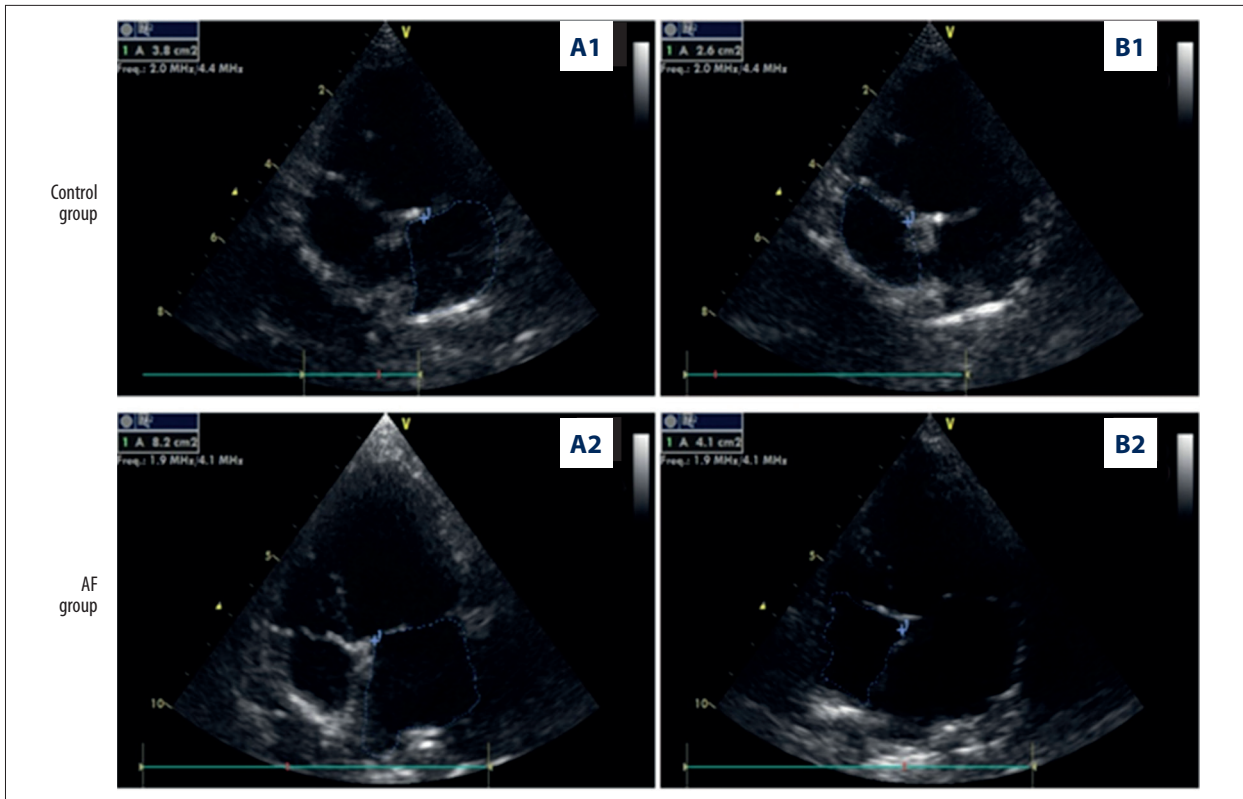


Figure 5. The areas of left atrium and right atrium were measured by echocardiography. (A1, A2) Measurement of the left atrial area; (B1, B2) Measurement of the right atrial area.

Table 1. Comparison of left and right atrial areas before and after successful establishment of atrial fibrillation (AF) model (cm²).

Index	Before successful establishment of AF model	After successful establishment of AF model	t-value	P-value
Area of the left atrium	3.80±0.08	8.20±0.83	-9.964	0.002
Area of the right atrium	2.75±0.96	4.52±0.44	-7.889	0.004

P<0.05 refers to statistical significance.

Table 2. Comparison of the left and right regional areas among the 2 groups (cm²).

Index	Control group	AF group	t-value	P-value
Left atrium area	3.72 ± 0.15	8.20±0.83	13.30	<0.05
Right atrium area	2.78 ± 0.18	4.52±0.44	8.85	<0.05

P<0.05 refers to statistical significance.

Morphological observation of the left atrial myocardium

Pathological changes in the left atrial myocardium

In the hematoxylin and eosin stained sections, the cardiomyocytes in the left atrium in the control group were structurally intact, neatly arranged, with clear nuclei, and filled with regular fiber network, whereas a moderate number of fibroblasts

with a regular shape were available in the intercellular substance. Meanwhile, in the AF group, the cardiomyocytes were enlarged, arranged disorderly, the nuclei had irregular size and abnormally altered, while some cells appeared obvious necrosis, vacuolar degeneration and granular degeneration, with loose intercellular substance, appearance of myocardial fibrosis and infiltration of inflammatory cells (Figure 6).

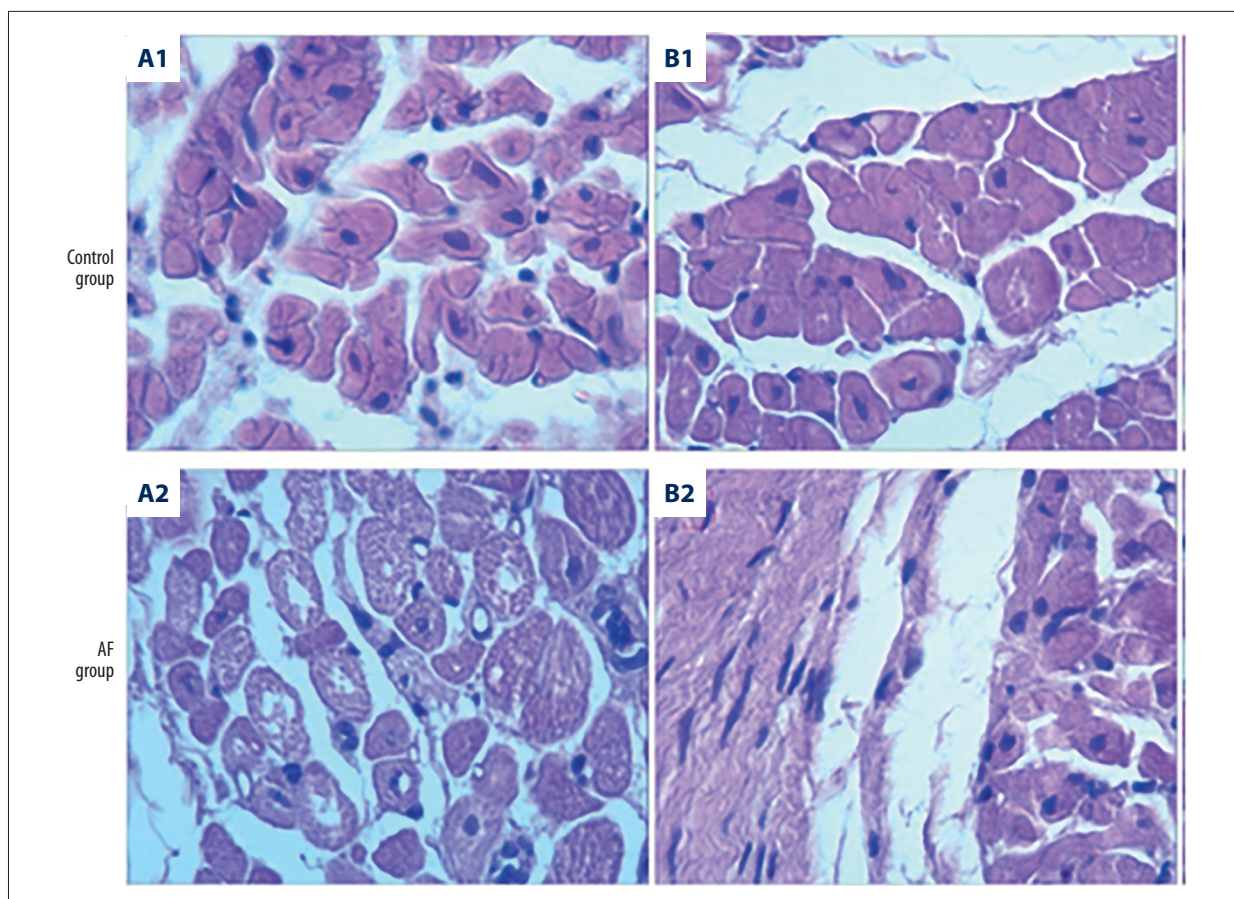


Figure 6. Pathological changes of atrial myocardial cells observed under a light microscope (400×). In the Control group (**A1**, **B1**) the cardiomyocytes in the left atrium were structurally intact, neatly arranged, with clear nuclei, and filled with regular fiber network. In the AF group, (**A2**) cardiomyocytes were obviously necrotic, with loose intercellular substance, vacuolar degeneration, and granular degeneration, (**B2**) fibrosis change of intercellular substance.

Ultrastructural changes of left atrial myocardium

The electron microscopy results of the left atrial myocardium revealed that the myofibrils in the left atrial myocytes in the control group were orderly arranged, with a normal chromatin structure in the nuclear membrane. Conversely, in the AF group, the ultrastructure of the left atrial myocytes was obviously abnormal, the myofibrils were severely degenerated, with severe pyknosis of the nuclei, and apoptosis of the cells was observed. Additionally, the endoplasmic reticulum appeared swelling, accompanied by disintegration of part of the myofibril and disordered muscle fibers (Figure 7).

Discussion

AF is the most common arrhythmia in clinical practice, which has become a cardiovascular epidemic disease [9,10]. In-depth studies of the mechanism of AF need to be based on animal models of AF. Animal AF models in the disease state

can reportedly be divided into the following types according to different modeling methods [11–13]: drug AF model, traumatic AF model, electrical stimulation AF model, ischemic AF model, and genetic engineering AF model. In the aforementioned methods for establishing of AF models, high-frequency atrial pacing is characterized by a high rate of inducing AF, simple preparation method, highly reproducible, and sustained AF is readily inducible and can be maintained for prolonged periods of time [14].

In 1995, Wijffels et al. [15] first reported the application of rapid atrial pacing in establishing a model of persistent AF, in which the pacing electrode was placed in the right atrial appendage, 300–600 times of pacing for 4–6 weeks. The establishment of the model can cause changes in the electric restructuring of the atrium and an increase in the atrial heterogeneity, which further facilitates the induction of AF.

In the present study, an animal AF model was established using high-frequency pacing, in which AF occurred without applying

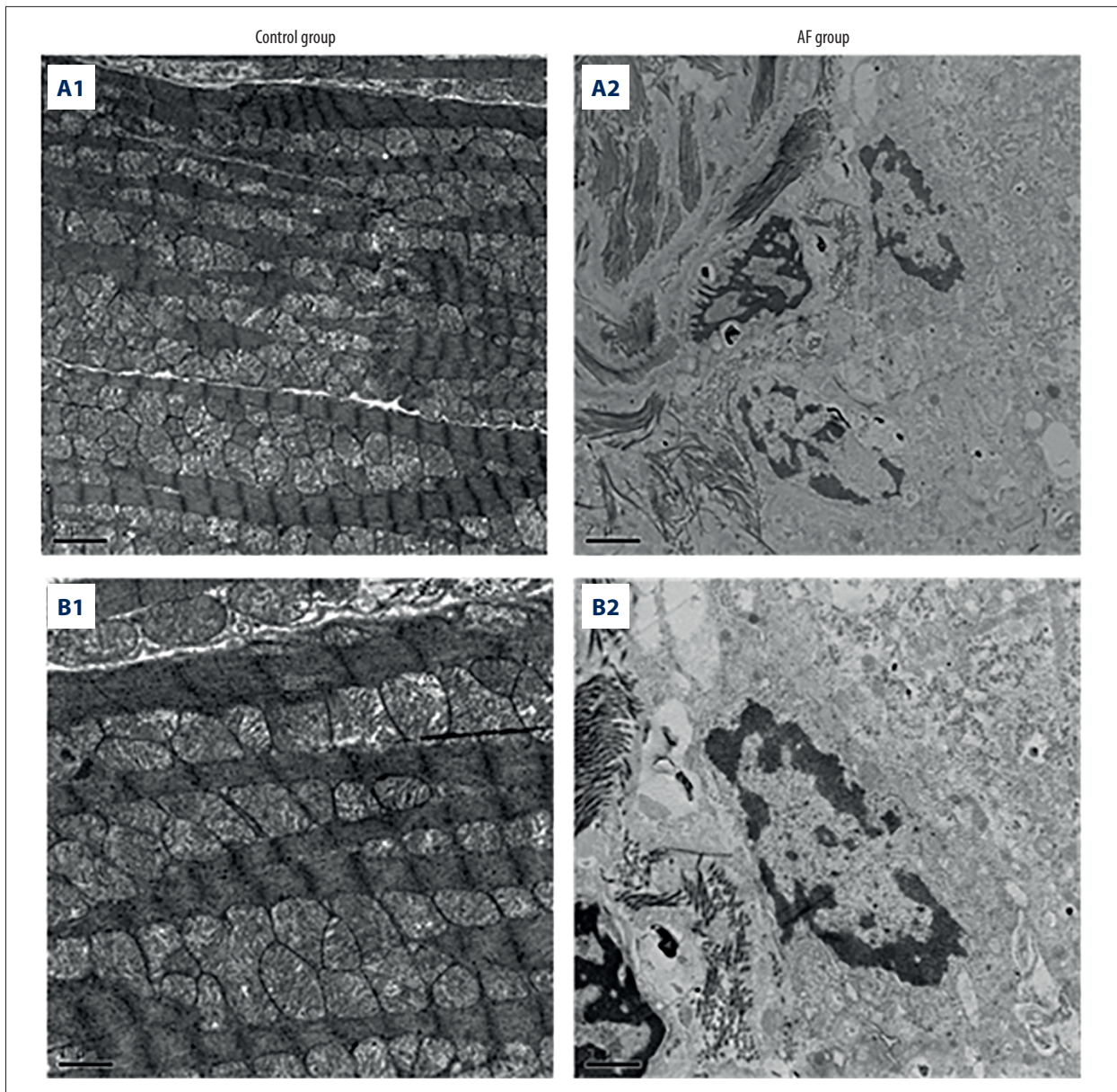


Figure 7. Observations of the ultrastructure of the left atrial myocardial cells in the Control group (**A1, A2**) and atrial fibrillation (AF) group (**B1, B2**) by electron microscopy. In the Control group, the myofibrils of left atrial myocytes were arranged orderly, and the chromatin structure of nuclear membrane was normal. In the AF group, the ultrastructure of the left atrial myocytes was obviously abnormal, with severe degeneration of myofibrillary, severe shrinkage of the nucleus, apoptosis of cells, enlargement of endoplasmic reticulum, and disorder of muscle fibers accompanied by disintegration of some muscle filaments.

programmed stimulation to the atrium. During the modeling process, a system with superior maneuverability was used for the first time to implant the thinnest bipolar guide wire 3830 active fixation lead into the right atrium of the dog in a simple, flexible, and accurate manner. This approach is innovative in modeling that promoted a higher success rate of implanting the lead in the atrium and facilitated the selection of pacing sites.

The insertable cardiac monitor is an implantable monitoring system for recording subcutaneous ECGs that can be activated automatically or even activated by the patient. It can be used for patients with clinical symptoms or conditions, as well as with increased risk of arrhythmia, and for patients who have experienced transient symptoms prompting the possibility of arrhythmia. Reveal LINQ is better than the previous generation of devices (Reveal XT) in data performance [8], especially in the monitoring of AF. It is characterized by precision and

fineness. In addition, Reveal LINQ reduces the size, improves the electrode coating, simplifies the implantation procedure, improves the quality and storage capacity of ECG, and becomes a reliable diagnosis and treatment tool for AF [7]. Another innovative highlight of this study is the use for the first time of Reveal LINQ to detect the occurrence and duration of AF during the establishment of the AF model. It can detect real-time AF sensitively, accurately, and efficiently, and provides long-range monitoring, to ensure the objectivity and accuracy of the data. Its memory device can automatically record the detected arrhythmia events and store arrhythmia event maps, thereby facilitating the review, collection, and analysis of ECG of arrhythmia events. In the animal AF model obtained through high-frequency atrial stimulation, the use of insertable cardiac monitor improved the efficiency of the dynamic detection of AF in the absence of programmed atrial stimulation employed to induce AF.

During the AF, a rapid and irregular atrial activity occurred, the intracellular calcium was overloaded due to an increase in the calcium influx; the atrial contractile function was affected, and the atrial load and pressure increased, which finally led to stretching of the atrial muscle fibers and passive expansion of the atrium as previously described [16]. This change provides a structural and pathophysiological basis for promoting the occurrence of AF [17]. In the present study, the areas of the left and right atrium were measured by echocardiography, and the results indicated that the areas of the left and the right atrium increased after the AF model was successfully established with right atrial pacing. The enlargement of the atrium suggests reconstruction of the atrial myocardium in animals, and this structural change is an important indicator of structural reconstruction in AF, which was also reported earlier [16]. Structural reconstruction of the atrium refers to the increase of interstitial tissue proliferation or fibrosis in the atrial muscle, the decrease of cell membrane stability, and the changes in the structure, morphology, and quantity of some organelles [18]. The morphological observations of the left atrial sections in the AF and control groups showed that the atrial structure of dogs in AF group had been reconstructed.

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In the present investigation, an advanced catheter control system and fine electrode leads were implemented in the establishment of a canine AF model to increase the efficiency and safety of modeling. In addition, an *in vivo* heart tracker was used to track the onset of AF, which enabled the provision of sensitive, convenient, accurate, efficient, and complete records for establishing the AF model. An innovative application of advanced and convenient instruments and equipment was realized based on a conventionally established AF model by high-frequency pacing, which provided accurate and efficient modeling methodology. In the future, we intend to conduct in-depth proteomics studies in dogs with AF, expecting to preliminarily screen out biomolecular markers of proteins that may be instructive, with high sensitivity, and good specificity. Meanwhile, correspondingly to the collected clinical samples, the expressions of the target differentially expressed proteins were verified in human specimens to determine their correlation with the clinical phenotype, aimed at the provision of protein biomolecular markers with high specificity for clinical treatment and a new target for dynamic monitoring of the prognosis in long-term clinical treatment.

Conclusions

The AF dog model was established by high-frequency atrial pacing. The 3830 bipolar solid atrial pacing leads were precisely implanted using the SelectSecure system, which improved the rate of successful implantation of electrodes. Therefore, the application of an insertable cardiac monitor Reveal LINQ improves the efficiency of monitoring the AF load, with high sensitivity, convenience, and accuracy.

Conflict of interests

None.

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