Importance of atrial surface area and refractory period in sustaining atrial fibrillation: Testing the critical mass hypothesis

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Objective: The critical mass hypothesis for atrial fibrillation (AF) was proposed in 1914; however, there have been few studies defining the relationship between atrial surface area and AF. This study evaluated the effect of tissue area and effective refractory period (ERP) on the probability of sustaining AF in an in vivo model.

Methods: Domestic pigs (n = 9) underwent median sternotomy. Epicardial activation maps were constructed from bipolar electrograms recorded from form-fitting electrode templates placed on the atria. Baseline ERPs were determined. ERP was lowered with a continuous infusion of acetylcholine (0.005-0.04 mg/Kg/min) until AF could be sustained after burst pacing. The atria were sequentially partitioned using bipolar radiofrequency ablation. ERPs were lowered using acetylcholine until AF could be sustained in each subdivision of atrial tissue. Each subdivision was further divided until AF was no longer inducible. At study completion, the heart was excised and the surface area of each section was measured.

Results: Over a range of ERPs from 75 to 250 ms, the probability of AF was correlated with increasing tissue area (range, 19.5-105 cm^2) and decreasing ERP. Logistic regression analysis identified shorter ERP ($P < .001$) and larger area ($P = .006$) as factors predictive of an increased probability of sustained AF (area under the curve of the receiver–operator characteristic = 0.878).

Conclusions: The probability of sustained AF was significantly associated with increasing tissue area and decreasing ERP. These data may lead to a greater understanding of the mechanism of AF and help to design better interventional procedures. (J Thorac Cardiovasc Surg 2013;146:593-8)

Atrial fibrillation (AF) remains a significant clinical problem and is the most common sustained arrhythmia in the United States, affecting over 2 million Americans.[1] It is a significant cause of morbidity and is thought to be responsible for 15% to 20% of all strokes.[1] In a population-based study, AF has been shown to be an independent risk for increased mortality.[2] Unfortunately, the mechanism underlying AF remains poorly understood.

In 1914, Garrey[3] hypothesized that a critical mass of atrial tissue was necessary to sustain AF. He theorized that multiple wavelets of electrical activity propagated through the atrium, activating it in an unorganized fashion, thus leading to fibrillation. Later, Weiner and Rosenbluth[4] introduced the concept of wavelength. Defined as the product of conduction velocity and refractory period, it is the minimum path length necessary for reentry in sustained AF. More recently, computer simulations of atrial sheets have demonstrated that the probability of fibrillation is dependent on increasing surface area.[5,6] Our laboratory has demonstrated the validity of the critical mass hypothesis in isolated canine atria.[7]

It is now understood that the mechanisms underlying AF are more complex and varied than multiple wavelets. AF may be the result of triggered activity, most commonly originating from the pulmonary veins.[8] It may also be the result of multiple wavelets of reentry as originally hypothesized, or it may be the result of a stable single rotor of reentrant activity that conducts in a fibrillatory manner.[9] Despite the complexity underlying the mechanisms of AF, successful procedures have been designed and implemented on the basis of this incomplete understanding. The Cox maze procedure was designed as an empirical operation to interrupt all possible reentrant circuits in AF by making incisions in both atria to create lines of conduction block.[10] This procedure has been very successful in treating AF, with success rates near 80% in preventing recurrent AF without antiarrhythmic drugs in a recent report.[11]

There remains a subset of patients for which the Cox maze procedure is not effective. Patients with large left atria are known to be susceptible to recurrent AF.[12] It is hypothesized that for patients with recurrent AF, the Cox maze

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Abbreviations and Acronyms
AF = atrial fibrillation
CT = computed tomography
ECG = electrocardiogram
ERP = effective refractory period

procedure does not divide the atria into small enough sections to prevent sustained AF.

Work from this laboratory demonstrated the effects of atrial surface area and changing effective refractory period (ERP) on the sustainability of AF in an in vitro model.[7] In isolated canine atria, larger atrial surfaces areas and shorter ERPs were associated with a high probability of sustained AF as predicted by the critical mass hypothesis. However, this has not been demonstrated in an intact animal model. The goal of this study was to evaluate the effect of tissue area, conduction velocity, and ERP on the sustainability of AF in an in vivo porcine model.

METHODS

Acetylcholine Dose Response

A preliminary study was conducted to establish the dose–response relationship between the ERP and acetylcholine systemically infused in the intact porcine model. The ERP was measured periodically during a continuous infusion of acetylcholine and for a period after acetylcholine was discontinued to establish typical recovery time for measured ERP. Three domestic pigs weighing 70 to 85 kg were used for this initial experiment. All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" (National Academy Press, Washington, DC). Each animal was premedicated with tiletamine/zolazepam (Telazol), ketamine, and xylazine, intubated, anesthetized with isoflourane, and monitored continuously throughout the procedure with electrocardiographic (ECG) and invasive arterial pressure recordings.

A median sternotomy was performed and a pericardial sling was created. Two bipolar electrodes were sutured to the right atrium. One bipolar electrode was used for pacing, and another bipolar electrode was used to record atrial electrograms. Baseline pacing thresholds were measured at the beginning of each experiment, and subsequent pacing was conducted at twice the pacing threshold. Eight stimuli with a basic cycle length of 300 ms (S1) followed by a single extrastimulus was used with variable cycle length (S2) were used to obtain ERP.

After baseline ERP was measured, a continuous infusion of acetylcholine was initiated through a 20-gauge catheter inserted into the left atrium through a purse-string suture. An initial dose of 0.005 mg/Kg/min was chosen on the basis of prior studies in dogs from the literature.[13] Infusion was continued for 20 minutes. ERP was measured at time 0 and at every 5 minutes during the infusion and recovery period on the right and left atria. After 10 minutes of stable sinus rhythm after infusion of acetylcholine, the dose of acetylcholine was increased and the process was repeated. This was repeated for doses of 0.005, 0.01, 0.015, and 0.02 mg/Kg/min. Occasionally, the atria would fibrillate. If this happened, the atria were allowed to fibrillate for 1 minute, after which an electrical cardioversion was performed.

Critical Mass Study

Nine domestic pigs weighing 60 to 85 kg were studied. Each animal was premedicated with tiletamine/zolazepam, ketamine, and xylazine, intubated, and anesthetized with isoflurane. The ECG and arterial pressure recordings were continuously monitored. Blood gases and electrolytes were determined and normalized every 20 minutes throughout the study.

Each animal had a set of atrial ablations performed through a median sternotomy (Figure 1). An iterative approach was used to induce AF. Before ablation, 2 bipolar pacing electrodes were sutured onto the right and left atria. Baseline ERP was measured using the single extrastimulus pacing technique. After ERP was measured, an attempt was made to induce AF by burst pacing. If necessary, a continuous infusion of acetylcholine was used to lower ERP until AF could be sustained. A set of 3 molded silicone plaques with a total of 252 unipolar electrodes were placed onto the epicardial surface to obtain epicardial electrograms, which were used to construct activation sequence maps. The electrode templates were constructed from a form-fitting silicone elastomer (Specialty Silicone Fabricators, Paso Robles, Calif) and contained 0.5-mm diameter silver electrodes (Pacific Wire & Cable, Inc, Santa Ana, Calif). The interelectrode distance was 5 mm. These plaques were secured with Rommel tourniquets to allow for consistent placement before and after each ablation. Electrograms were acquired during normal sinus rhythm, paced rhythm at 180 beats/min, and for at least 10 seconds during each episode of AF and used for offline analysis after each study.[7] Data were recorded at a gain of 125 and frequency response of 0.5 to 500 Hz and digitized at 1000 Hz. Activation times were calculated by determining the maximum negative instantaneous rate of voltage change over time. Activation maps were displayed on a 3-dimensional model of the atrial surface. Conduction velocity was calculated from the epicardial activation maps during paced rhythm. Next, the atria were subdivided with transmural linear ablations created by a bipolar radiofrequency ablation device (Isolator Atricure, Cincinnati, Ohio) (Figure 1). The process of measuring ERP and inducing AF was repeated in each subdivision until AF could no longer be sustained despite maximal doses of acetylcholine. Minimal ERP in each subdivision of atrial tissue was estimated using the minimal AF cycle length from the electrogram recordings for each instance of AF. It has been shown that this method accurately estimated the ERP during AF in an isolated canine atrial model.[14] During episodes of AF, these estimated minimal ERPs were used in the analysis for the study. This was done to obtain the minimal ERP in a given tissue section.

When the atrium did not fibrillate, the ERP was measured directly. To measure ERP, we determined pacing thresholds from each of the pacing electrodes. Subsequent pacing was carried out at twice threshold. After each ablation, thresholds were remeasured. Eight stimuli with cycle lengths of 300 ms (S1) followed by a single extrastimulus was used with variable cycle lengths (S2) used to manually obtain ERP. To induce AF in the instances in which a single extra beat did not induce AF, we used burst pacing with a cycle length set to 45 ms. Burst pacing continued for 30 seconds, and sustained AF was defined as AF that lasted longer than 30 seconds.

If the section of atrium failed to sustain AF after 2 attempts, a continuous infusion of acetylcholine was used to lower the ERP of the atria. A catheter was placed through a purse-string suture directly into the left atrium to minimize the exposure of the drug to cholinesterases before reaching the coronary circulation. The starting dose was 0.005 mg/Kg/min and was increased in increments of 0.005 mg/Kg/min to a maximum dose of 0.04 mg/Kg/min. Acetylcholine was infused for 5 minutes before measurements were begun to allow for the ERP to stabilize. During infusion of acetylcholine, intravenous infusion of phenylepherine (1-2 mg/ kg/min) was used to maintain a mean blood pressure above 50 mm Hg.

The lesion set to subdivide the atrium is shown in Figure 1. All ablations were performed with a bipolar radiofrequency clamp device. This technology has been shown to reliably create transmural lesions and bidirectional conduction block and at the same time preserve the circulation to the atrial tissue.[15] An initial ablation was performed to encircle a cuff of atrial tissue around the left and right pulmonary veins, respectively. The atrial surface area outside these ablation lines served as the baseline surface area for induction of AF. The first division of atrial surface area was obtained by creating a line of ablation extending from the left pulmonary vein ablation