Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 56, No. 21, 2010
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.05.051

Roles of the Left Atrial Roof and Pulmonary Veins in the Anatomic Substrate for Persistent Atrial Fibrillation and Ablation in a Canine Model

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Objectives The aim of this study was to establish the electrophysiological consequences of pulmonary vein encircling ablation (PVEA) and linear left atrial roof ablation (LARA) for the atrial fibrillation (AF) substrate in an experimental model.

Background Sequential application of ablation lesions is often used in the management of AF, almost always incorporating PVEA and LARA.

Methods Atrial tachypacing (400 beats/min, 5 weeks) was used to create an AF substrate in 13 dogs. PVEA and LARA were applied in randomized order. Regional atrial refractoriness, AF vulnerability, AF duration, and activation during AF were assessed before and after applying ablation lesion sets.

Results PVEA failed to terminate AF or affect AF duration (742 ± 242 s before vs. 627 ± 227 s after PVEA) but decreased AF vulnerability to single extrastimuli from 91 ± 4% to 59 ± 5% ($p < 0.001$) by increasing effective refractory periods at sites with suppressed AF induction (from 78 ± 4 ms to 102 ± 8 ms, $p < 0.01$). LARA terminated AF in 67% of dogs ($p < 0.05$ vs. PVEA) and reduced AF duration (from 934 ± 232 s to 322 ± 183 s, $p < 0.01$) without affecting AF vulnerability. Baseline AF mapping showed left atrial (LA)-dominant complex reactivations (LA 9.4 ± 0.9 vs. right atrial 1.1 ± 0.3 reactivations/500-ms window, $p < 0.001$), with the LA roof frequently involved in re-entry circuits (44 ± 9% of LA reactivations). LARA terminated AF by interrupting LA roof reactivation circuits. In 5 of 13 cases, macro–re-entrant tachycardias (usually perimitral) occurred after LARA eliminated persistent AF.

Conclusions Both PVEA and LARA had beneficial but limited actions in this canine model. LARA suppressed AF perpetuation by interrupting LA roof reactivation, without affecting AF vulnerability. PVEA suppressed AF initiation by prolonging regional effective refractory period but failed to affect the AF-perpetuating substrate. These findings indicate the need to systematically study individual stepwise components to refine AF ablation procedures. (J Am Coll Cardiol 2010;56:1728–36) © 2010 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is a very common, therapeutically challenging arrhythmia (1,2). Although left atrial (LA) ablation procedures targeting the pulmonary veins (PVs) are effective for treating paroxysmal AF (3,4), PV isolation alone has limited efficacy in persistent or permanent AF (4–6). Additional ablation lines, often involving left atrial roof ablation (LARA) as a second step, improve procedural outcomes (7,8) and are effective in managing persistent AF (9). Studies of the "stepwise ablation approach" have provided insights into some aspects of the contribution of ablating various regions in human AF (10,11). However, detailed repeated analyses of changes in electrophysiological properties and atrial activation after each step are difficult to

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Manuscript received December 24, 2009; revised manuscript received April 8, 2010, accepted May 18, 2010.

obtain during clinical procedures. There has been no systematic analysis of the effects of components of stepwise procedures for AF ablation in animal models. We hypothesized that such components could have discrete effects on the AF substrate, and studied the consequences of PV encircling ablation (PVEA) and LARA in dogs with a persistent AF substrate. We chose this model because of its potential relevance to the persistent AF substrate in humans, recognizing that some forms of clinical AF (e.g., paroxysmal AF) likely have very different mechanisms.

Abbreviations and Acronyms

AF = atrial fibrillation
DF = dominant frequency of fast Fourier–transformed signals
ERP = effective refractory period
LA = left atrial
LARA = left atrial roof ablation
PV = pulmonary vein
PVEA = pulmonary vein encircling ablation
RA = right atrial
S1 = basic stimulus
S2 = premature stimulus

Methods

Experimental groups. Animal-handling procedures were approved by the local animal research ethics committee. PVEA and LARA were performed in randomized order in 13 mongrel dogs weighing 25.6 to 34.0 kg. In 7 dogs (group 1), PVEA was applied first, and in 6 dogs (group 2), LARA was applied first. Dogs were subjected to atrial tachypacing, as previously described (12,13). Dogs were anesthetized with intravenous ketamine (5.3 mg/kg), intravenous diazepam (0.25 mg/kg), and halothane (1.5%). A bipolar pacing lead was inserted into the right atrial (RA) appendage and connected to a pacemaker (SIP 501, Star Medical, Tokyo, Japan) in the neck. After 24-h post-operative recovery, 5-week atrial pacing at 400 beats/min was initiated. Oral digoxin (0.25 mg/day) was administered to control ventricular response. Open-chest electrophysiological studies were performed after 5 weeks.

Study protocols. At open-chest study (median sternotomy), atrial pacemakers were deactivated. Dogs were anesthetized with subcutaneous morphine (2 mg/kg) and alpha-chloralose (120 mg/kg load, 29.25 mg/kg/h) and ventilated mechanically. Body temperature was maintained at 37°C. Bipolar electrodes were hooked into the RA and LA appendages. Silicon sheets containing 240 bipolar electrodes were sutured onto atrial surfaces for mapping (14). Six group 1 and 5 group 2 dogs (85% of all study animals) were in persistent AF when atrial pacemakers were deactivated; AF was cardioverted before baseline electrophysiological studies. PVEA or LARA was then performed, and electrophysiological studies were repeated. Atrial effective refractory period (ERP) was measured with 10 basic stimuli (S1s) followed by premature extrastimuli (S2s) (all stimuli 2 × threshold current 2-ms pulses) in 5-ms increments. At least 1 min of pacing was applied at each basic cycle length before ERP determination to ensure steady-state conditions, a 1-s pause was used to observe the response to S2s, and the ERP was determined by incrementing from noncapturing S1-S2s so that captured beats produced minimal interference with the basic frequency. The longest S1-S2 failing to capture defined the ERP. ERPs were measured at basic cycle lengths of 150, 200, 250, 300, and 360 ms in the LA and then RA appendages and at a basic cycle length of 300 ms at 6 additional sites in the following order: RA posterior wall, RA inferior wall, RA Bachmann's bundle, LA Bachmann's bundle, LA inferior wall, and LA posterior wall. AF vulnerability was the percent of atrial sites at which AF >1 s was induced by S2s. AF was defined as an irregular atrial arrhythmia at >400 beats/min. To estimate mean AF duration in each dog (12–14), AF was induced with 1- to 10-s burst pacing (10 Hz, 4 × threshold current). Persistent AF (>30 min) was terminated by direct current cardioversion. If persistent AF was induced twice, ablation procedures were performed 5 min into a third persistent AF episode to determine the ability to terminate AF. Activation was assessed as previously described (14) over a 500-ms window at baseline and after each ablation step for each AF episode.

The frequency-content of fibrillatory activity was analyzed by fast Fourier transformation of bipolar potentials over 40-s periods (15). The dominant frequency (DF) at each electrode was based on the peak in the power spectrum between 5 and 20 Hz.

Ablation. Ablations were performed during persistent AF when it was reproducibly inducible (9 dogs) or otherwise during sinus rhythm. PVEA was performed on the antrum of both right and left PVs about 0.5 to 1.0 cm from the ostia by delivering 32.5-W applications via a bipolar epicardial radiofrequency clamp. Each PV was mapped epicardially on 6 segments (anterior and posterior cranial, anterior and posterior caudal, ventral, and dorsal) with a bipolar electrode probe for the presence of PV potentials. Completed PVEA was confirmed by loss of PV responses to LA stimulation and of LA response to PV stimulation at all PV sites distal to the ablation line.

For LARA, a bipolar epicardial radiofrequency ablation pen device was inserted posterior to the left atrium above the left superior PV and advanced to above the right superior PV. Radiofrequency energy (35 W through 100-Ω resistance) was delivered point by point for 30 s at each site from the right to left superior PVs. A completed LARA line was confirmed by discrete double potentials along the ablation line.

Data analysis. Continuous variables are expressed as mean ± SEM. Fisher exact tests were used to compare frequencies. Paired *t* tests were used to compare paired within-group observations, 2-way repeated-measures analysis of variance was used to analyze the main effects of ablation on ERPs across basic cycle lengths and atrial regions, and analysis of variance with Bonferroni-corrected *t* tests was used to evaluate DF changes with ablation and PVEA effects on ERP according to vulnerability responses. All data were normally distributed, except AF duration,