Thoracic vein ablation terminates chronic atrial fibrillation in dogs

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METHODS

Six female mongrel dogs (body wt, 21–28 kg) underwent a two-stage surgical procedure that was approved by the Institutional Animal Care and Use Committee. The procedures conformed to American Heart Association guidelines.

First surgery and pacing protocol. All dogs received isoflurane general anesthesia via an endotracheal tube. A left lateral thoracotomy was then performed in the 4th intercostal space for optimal visualization of the left superior PV (LSPV). A bipolar screw-in lead was affixed to the LSPV, and the distal end was connected to a Medtronic Itrel neurostimulator. The pericardium was not disrupted. After a 24-h recovery period, the stimulator was programmed to burst pace at a pacing interval of 50 ms for 5 s followed by a 2-s period of no pacing (26). In the first two dogs, a Guidant active-fixation electrode was advanced under fluoroscopic guidance via the right internal jugular vein into the RA to monitor rhythm and verify atrial response to LSPV pacing. The remaining four dogs had only LSPV electrode placement, and rhythm monitoring was recorded intermittently via electrodes at 0.5-Hz intervals.

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placed on the skin. The dogs were checked on a weekly basis for AF induction. The stimulator was turned off to verify underlying rhythms. If AF was documented, the stimulator was kept off for 48 h to document the maintenance of AF. If AF was sustained for >48 h, the pacemaker was turned back on and the dogs were scheduled for a second surgical procedure for mapping and ablation. If sinus rhythm recurred within 48 h, the stimulator was programmed back on to the same protocol and the rhythm was reexamined 1 wk later.

Second surgery for mapping and ablation. While under isoflurane anesthesia via endotracheal tubes, the dogs were placed in the supine position. The chests were opened via a median sternotomy, and the pericardium was incised and reflected back for exposure of the atrial-PV junction. Bipolar hook electrodes were inserted into the RA, LA, VOM, LSPV, left inferior PV (LIPV), right superior PV (RSPV), and right inferior PV (RIPV) for continuous recording of activity throughout the procedure. Simultaneous computerized mapping of one or more PVS and both atria was also recorded (27). The ablation catheter consisted of seven electrodes at 2-mm spacing with a malleable shaft that could encircle the PVS and apply RF energy to the anterior and posterior aspects. In two dogs, the catheter was hooked to the Cobra RF ablation system (Boston Scientific; Ref. 12) for delivery of RF energy (an average of 60 s per lesion). The temperature was set at 65°C, and the power was set at 50 W. In the other dogs, a 4-mm-tip quadripolar ablation catheter was employed as a roving probe using a Radionics RF generator to create lesions encircling the PVS and on the VOM. RF energy was applied to the epicardial surface along the VOM and each PV within 5 mm of the atrial junction for 1 min at 10 W and 60°C for each application. Electrical recordings were made to ensure that the PVS were electrically isolated. The heart was then fixed with 4% formalin for 1 h and stored in 70% alcohol. The PVS and the tissues overlying the VOM were excised and paraffin embedded. Sections (5 μm) were stained with hematoxylin and eosin for light-microscopic examinations.

Computerized mapping and bipolar electrograms. Computerized mapping was performed with four electrode patches that were connected to a Unemap 1,792-channel mapping system (Auckland, New Zealand; Ref. 27). Up to four electrode patches were used in the study. Each patch had 448 electrodes, and the interelectrode distance was 1 mm; the patch therefore covered a 1.5 × 2.7-cm area. A patch covering the area between the left atrial appendage and the left PVS was used to map VOM activity. The electrode overlying the anterior aspect of the PV-LA junction was used to map the electrical activity in that area. Electrodes were spaced 1 mm apart in 16 columns and 28 rows; 3 channels from 1 electrode patch recorded the surface ECG. Simultaneous computerized mapping was performed of the RA, LA, VOM, and one or more PVS (LSPV, LIPV, RSPV, RIPV) at baseline and after ablation. Each recording consisted of 8 s of data, which was then analyzed offline according to previously published methods (26). The AF cycle length was calculated based on data obtained from the bipolar electrodes of the mapping system and not from the bipolar hook electrodes. The bipolar electrode used in the mapping system has a small (1 mm) interpolar distance that can register discrete activations even during AF. Therefore, we used bipolar electrograms from the mapping system for cycle length calculations (26). The cycle length is the mean of all AF cycle lengths within a specified area. This method has been used in the past to extract periodicity in noisy time-series signals (4). Activation cycle lengths were determined after each RF ablation. Data are presented as means ± SD. Student’s two-tailed t-tests were used to compare the means. Correlation coefficients were calculated between the activation cycle lengths and the numbers of ablations performed. A P value of ≤0.05 was considered significant.

RESULTS

RF ablation of sustained AF. Rapid pacing from the LSPV induced sustained AF within 30.6 ± 6.5 days (Fig. 1). There was no clinical evidence of heart failure in any dog. The dogs underwent RF ablation 17.3 ± 8.5 days (7–30 days) after documentation of sustained AF. Successful electrical isolation was documented by the elimination of electrical activity in the SVC and PV (Fig. 2). The ligament of Marshall is located on the epicardium. Successful ablation results in obvious discoloration and charring of this epicardial structure. Four dogs converted to sinus rhythm during RF ablation, whereas two dogs converted within 90 min of completion of RF application (Fig. 3A). In one of the latter two dogs, AF spontaneously converted to atrial tachycardia 78 min later and then to sinus rhythm in 9 min. In the remaining dog, sustained AF converted to atrial tachycardia after thoracic vein isolation. Burst pacing from the RA resulted in tachycardia termination and conversion to sinus rhythm.

Rapid right atrial pacing was successful in reinducing AF in all dogs. However, all induced AF episodes either terminated

Fig. 1. Induction of sustained atrial fibrillation (AF) by pacing the extrapericardial portion of the pulmonary vein (PV). A: intracardiac electrogram recorded by the pacemaker lead implanted at the right atrial appendage. PACing lead was connected to a Guidant Discovery II pacemaker. When interrogated, the pacemaker programmer can print out real-time electrograms from the right atrial apex. Atrial (A) and far-field ventricular (V) electrograms are indicated. This electrogram was recorded at the beginning of the pacing protocol within 2 days after surgery. Times when the Medtronic Itrel pacemaker started (on) and ended (off) a cycle of pacing are shown by arrows. Sinus rhythm was present between off and on markers. B: electrogram recorded 4 wk later when the Itrel pacemaker was turned off. Electrogram from the right atrial appendage shows AF. Itrel pacemaker was left in the off mode. C: the dog was still in AF when we returned 48 h later.
spontaneously within 60 s (Fig. 3B) or converted to atrial tachycardia before termination (Fig. 4). The average cycle length of reinduced AF was significantly (P < 0.01) slower (183 ± 31.5 ms) than at baseline (106 ± 16.2 ms).

Effects of RF ablation on AF activation patterns. Multiple RF applications (n = 15 ± 4 applications/dog) resulted in progressive lengthening of the activation cycle from 95 ± 8.5 ms at baseline to 126 ± 24.6 ms after ablation in RA and from 83 ± 11.4 ms at baseline to 99.4 ± 15.1 ms after ablation in LA. There was a significant positive correlation between the number of ablations and the activation cycle length (RA: r = 0.90, P < 0.01; LA: r = 0.95, P < 0.01).

Computerized mapping demonstrated multiple reentrant wave fronts within the atria. The RA predominantly demonstrated large and fairly organized wave front activity and at times was passively activated from the LA. The SVC was consistently activated passively from the RA. The LA demonstrated multiple small, wandering wavelets with predominantly two identifiable activation patterns: focal activity that 1) propagated from the area of the VOM outward, and 2) originated from PVs and propagated toward the LA and VOM. These findings are consistent with our previous reports (5, 27). After RF ablation, electrical activity within the PV was no longer present (Fig. 2D). Furthermore, when post-RF left atrial activity was analyzed, no wave front activity was noted that extended from the region of the PVs.

Effects of RF ablation on bipolar hook-electrode recordings. In total, 64 bipolar hook-electrode recordings were analyzed (6 SVC, 8 LSPV, 8 RSPV, 6 LIPV, 6 RIPV, 10 VOM, 10 LA, and 10 RA). Activation patterns from the PVs and the VOM were complex and highly fractionated and were defined as frequent deflections that occurred within <40 ms of one another. PV and VOM (84.7 ± 11.8 ms) activations were consistently faster than the atria. SVC (130.1 ± 19.2 ms) activation appeared slower and more organized compared with the atria and PVs (LSPV, 81.1 ± 9.3; LIPV, 78.8 ± 12.5; RSPV, 80.7 ± 8.2; RIPV, 83.5 ± 16.1 ms). As in previous studies, mean cycle lengths confirmed an activation rate gradient between PVs and
the atria. At the end of ablation, activation cycle lengths between the atria and between the LA-PVs (LSPV, RSPV, RIPV, LIPV, and VOM) were not significantly different.

**Histopathology of RF lesions.** Transmural lesions were observed in all specimens of the PVs. The Marshall bundles in the ligament of Marshall were also successfully ablated. Typical examples of transmural RF lesions in the PV (Fig. 5A) and the destruction of the Marshall bundle (Fig. 5B) are shown. RF application resulted in hypereosinophilia, basophilia, and loss of cellular details.

**DISCUSSION**

In this study, we show that rapid electrical stimulation from the LSPV could induce sustained AF. Therefore, pericardial disruption and pericarditis (14) are not the cause of AF in this model. Using this new model, we demonstrated that thoracic vein isolation converted canine sustained AF into sinus rhythm and prevented the reinduction of AF. These findings suggest that thoracic veins are important in the maintenance of AF in this model.

**Electrical remodeling and sustained AF.** Traditionally, the mechanisms and maintenance of AF are thought to result from electrical and morphological remodeling within the atria. However, it has become increasingly evident that muscle sleeves within the thoracic veins generate rapid, repetitive activities that serve as triggers in the generation of AF. These rapid activations propagate to the atria and initiate reentry. In normal atria, reentry may self-terminate and result in paroxysmal episodes of AF. Various studies (6, 9, 23) have demonstrated that elimination of these triggers (rapid activations) with RF application results in elimination of paroxysmal AF. For chronic AF, it is generally thought (24) that atrial remodeling provides the necessary substrate for reentry that sustains AF (AF begets AF).

Wijffels et al. (24) reported that sustained (>24 h) AF can be induced in goats with 7 days of rapid pacing. However, the most apparent shortening of the AF cycle length and atrial effective refractory periods occurred within the first 24 h of pacing. Lee et al. (15) reported that atrial effective refractory periods shortened significantly after 1 day of rapid atrial pacing in dogs. These studies show that electrical remodeling occurs within 24 h after rapid atrial pacing in both animal models.

Because atrial remodeling is thought to underlie the mechanism of chronic AF, abolition of triggers within the thoracic
veins would not be sufficient to terminate AF. A maze procedure is needed to prevent sustained AF (3). Kress et al. (13) were able to simplify the maze procedure by focusing on PV isolation to terminate chronic AF in a canine model. In the latter study, endocardial ablation was used to isolate the PV and the left atrial appendage. In addition, the authors placed connecting lines between PVs and between the left PV and left atrial appendage. The latter line might have included a portion of the VOM. They were able to terminate chronic canine AF and render it noninducible. In our study, we were able to termianate AF by thoracic vein isolation alone without isolating the left atrial appendage or placing connecting lines between the PVs. Because it was not possible to reinude AF in these animals, electrical remodeling of the atria alone does not appear to be sufficient to sustain AF in this model.

**Importance of thoracic veins in maintenance of sustained AF.** During sustained AF in humans (7) and dogs (10, 17, 26), the LA activates faster than the RA. Small areas of particularly rapid activations can be identified in the PV orifice in humans (7) and in the posterior LA in dogs (17). Williams et al. (25) reported that PV isolation without extensive atrial ablation converted AF to sinus rhythm in 34 of 42 patients (81%) with chronic AF. It was also possible to achieve electrical isolation of the PVs and terminate chronic sustained AF (16, 19, 22). However, not all patients had successful termination with PV isolation. One possible reason for a high rate of failure in some series is that the substrates of sustained AF in many patients are not limited to PVs. Other thoracic veins such as the VOM are also responsible for the maintenance of AF. Complete ablation of these thoracic veins might result in a higher rate of cure. This possibility remains to be proven by studies of VOM isolation in humans. Furthermore, complete isolation of the PVs might be a difficult task if catheter-ablation techniques are used. In this study using animal models, we were able to perform complete thoracic vein isolation via an epicardial approach, which resulted in termination of AF in all dogs studied. Multiple episodes of nonsustained AF were induced after RF ablation to document the absence of substrates for sustaining the AF. Our results strongly support the idea that thoracic veins are important not only as triggers of paroxysmal AF but also in the maintenance of sustained AF (1). These results also suggest that complete thoracic vein isolation might be necessary to cure chronic sustained AF.

**How does thoracic vein isolation prevent AF?** We previously demonstrated (27) that there are focal discharges from the PVs during chronic sustained canine AF. Focal discharges are also present in the PVs and VOMs during AF in dogs with congestive heart failure (18). Rapid and fractionated activity is also present within the VOM during permanent AF in humans (8). Because the muscle sleeves of the VOM and PV are insufficiently thick to maintain a transmural reentrant wave front, these focal discharges are most likely due to automaticity and triggered activity, which are known to develop in the atrial myocardium (24). RF isolation of the PVs and VOMs results in termination of AF in all dogs studied. Complete ablation of the PVs and VOMs might result in a higher rate of cure. This possibility remains to be proven by studies of VOM isolation in humans. Furthermore, complete isolation of the PVs might be a difficult task if catheter-ablation techniques are used. In this study using animal models, we were able to perform complete thoracic vein isolation via an epicardial approach, which resulted in termination of AF in all dogs studied. Multiple episodes of nonsustained AF were induced after RF ablation to document the absence of substrates for sustaining the AF. Our results strongly support the idea that thoracic veins are important not only as triggers of paroxysmal AF but also in the maintenance of sustained AF (1). These results also suggest that complete thoracic vein isolation might be necessary to cure chronic sustained AF.

**Limitations.** It is possible that other models of chronic pacing-induced AF (right and left atrial pacing) may also be terminated by PV isolation as was the case in the present model of sustained AF induced by chronic PV pacing. However, we do not have data from this study to test that hypothesis. Our dogs have only been in AF for <30 days. It is possible that

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**Fig. 5. Transmural lesion induced by RF ablation.** A: muscle sleeves of PV. There is full-thickness coagulation necrosis of myocardial cells characterized by increased basophilia, loss of nuclei, and loss of cellular details (hematoxylin and eosin stain, ×80 magnification). B: effects of ablation on the atrial wall. There is basophilia of the atrial myocardium (AM) and nerves (N), dilatation of veins (V), and hypereosinophilia of the Marshall bundle (MB) after RF ablation. Whether the tissue appears hyperesosinophilic or basophilic depends on the magnitude of the thermal damage (hematoxylin and eosin stain, ×16 magnification).
dogs with longer or shorter AF duration might respond differently to the thoracic vein isolation than these dogs. Schauerte et al. (20) previously demonstrated that transvascular RF catheter ablation of the parasympathetic pathways can abolish vagally mediated AF. It is possible that some of the results of this study were due to disruption of the fat pads that contain the parasympathetic nerves. Because we did not perform vagal stimulation in this study, we do not have data to prove or disprove this hypothesis.

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