Received: 13 July 2021 | Accepted: 9 March 2022

DOI: 10.1111/jvim.16412

STANDARD ARTICLE

Journal of Veterinary Internal Medicine Open Access

ACVIM American College of Veterinary Internal Medicine

Feasibility of electroanatomic mapping and radiofrequency catheter ablation in Boxer dogs with symptomatic ventricular tachycardia

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Funding information
American College of Veterinary Internal Medicine, Grant/Award Number: Resident Fund; Companion Animal Research Fund; Winkelman Family Fund in Cardiovascular Research

Abstract

Background: Treatment for Boxers with ventricular tachycardia (VT) is limited. Electroanatomic mapping (EAM) facilitates identification of arrhythmogenic substrate for radiofrequency catheter ablation (RFCA).

Objective: Describe the use of EAM to guide RFCA in Boxers with VT.

Animals: Five client-owned Boxers with symptomatic VT or persistent VT despite antiarrhythmic medications.

Methods: Case series evaluating clinical, EAM, and before and after RFCA Holter data.

Results: Sustained VT was inducible in 3 dogs, but required aggressive stimulation protocols. Low-voltage areas consistent with electroanatomic scar were found in 2 dogs, located at the right ventricular (RV) outflow tract and cranial RV. Two dogs had a focal activation pattern of VT and 1 dog had a reentrant mechanism. After RFCA, all dogs no longer collapsed and had fewer runs of VT, 3 of which had 0 runs of VT. Number of ventricular premature beats increased in 3 dogs and decreased in 2 dogs, 1 of which had nearly complete resolution of all arrhythmias. Procedural complications included ventricular fibrillation (n = 2) with successful defibrillation, bruising or hemorrhage at the vascular access site (n = 4), retroperitoneal hemorrhage (n = 1), aortic and mitral regurgitation (n = 1), onset of frequent supraventricular tachycardia (n = 1), and persistent right pelvic limb lameness (n = 1).

Conclusions and Clinical Importance: Electroanatomic mapping and RFCA are feasible in Boxers with VT. Based on this small cohort, RFCA may help decrease runs of

Abbreviations: %VE, percent of total ventricular beats consisting of ventricular premature complexes; AAD, antiarrhythmic drug; ARVC, arrhythmogenic right ventricular cardiomyopathy; EAM, electroanatomic mapping; EGM, electrogram; LBBB, left bundle branch block; LV, left ventricle; OTVT, outflow tract ventricular tachycardia; PES, programmed electrical stimulation; RBBB, right bundle branch block; RFCA, radiofrequency catheter ablation; RV, right ventricle; RVOT, right ventricular outflow tract; VA, ventricular arrhythmia; VE, ventricular ectopy; VPC, ventricular premature complex; VT, ventricular tachycardia.

Alexandra V. Crooks and Weihow Hsue are co-first authors.

VT and improve clinical signs. The anatomic substrate and electrophysiologic mechanisms are variable and require further study.

KEYWORDS

arrhythmia, arrhythmogenic right ventricular cardiomyopathy, canine, electrophysiology, syncope, veterinary

1 | INTRODUCTION

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a familial myocardial disease of Boxer dogs and humans that impairs the function of desmosomes, which maintain adhesion between cardiac cells.[1,2] Desmosomal abnormalities associated with striatin[3] or other genetic mutations cause mechanical and electrical uncoupling between cells that leads to cardiac myocyte atrophy with fatty or fibrofatty replacement,[4-6] generating scar tissue that may provide the electroanatomic substrate for ventricular arrhythmia (VA) formation and ventricular dysfunction.[5-8] In dogs, ARVC is characterized by a high incidence of VA, syncope, and sudden death.[4,9-11] Documentation of VA in a Boxer without other identifiable causes typically results in presumptive diagnosis. Although QRS morphology may vary, ventricular premature complexes (VPCs) and ventricular tachycardia (VT) typically have a left bundle branch block (LBBB) morphology (ie, positive deflection in leads II, III, and aVF) suggestive of origin from the right ventricle (RV).[11,12] Most dogs have apparently normal echocardiograms, but some may develop myocardial dysfunction.[8,9,11,13]

Antiarrhythmic medications, the mainstay of treatment in dogs, may not be tolerated or may provide inadequate arrhythmia control.[11,14,15] When this outcome occurs in human patients, radiofrequency catheter ablation (RFCA) is offered to decrease VT burden.[6,16] This approach involves applying thermal energy to cause tissue necrosis,[17] with the goal of modulating the arrhythmogenic substrate to prevent initiation or perpetuation of VA.[18] Previous studies of RFCA in dogs have focused on supraventricular tachyarrhythmias, including accessory pathway-mediated tachycardia, focal atrial tachycardia, and atrial flutter; VT ablation has been reported only once in an English Bulldog.[19-24] These procedures relied on fluoroscopic guidance to anatomically position catheters. In contrast, 3-dimensional (3D) electroanatomic mapping (EAM) utilizes magnetic- and impedance-based localization methods to record intracardiac electrical activations in relation to anatomic location, allowing generation of 3D maps that can reflect scar distribution and depolarizing sequence of arrhythmias.[25] This approach allows more precise localization of critical sites of complex arrhythmias and is routinely used to guide RFCA in people with ARVC.[26,27] Although EAM has been performed in experimental settings in dogs,[28] to our knowledge, EAM has not been performed in client-owned dogs with spontaneously occurring arrhythmias.

Using a clinical population of Boxers with symptomatic or persistent VT despite antiarrhythmic treatment, our objectives were to: (a) evaluate the clinical features and electroanatomic substrate of Boxers with presumptive ARVC and (b) describe the use of EAM to guide RFCA in 5 dogs.

2 | MATERIALS AND METHODS

2.1 | Animals

All procedures were approved by the Institutional Animal Care and Use Committee at the University of Pennsylvania. Five Boxer dogs were prospectively enrolled between August 2019 and February 2021. Eligible dogs had clinical signs of collapse and evidence of VT (≥3 consecutive VPCs at a heart rate >180 beats per minute), and most dogs either could not tolerate or had persistent VT despite antiarrhythmic treatment. Dogs with other clinically relevant structural cardiac or systemic diseases were excluded.

Each dog underwent physical examination, CBC and serum biochemistry analysis, striatin testing, echocardiography, 5-minute ECG, and before and after the procedure 48-hour Holter monitoring (except in 2 dogs with shorter duration Holters studies [17-35 hours] because of technical issues, poor client compliance, or clinician preference). Dogs were negative for the striatin mutation if they had 2 copies of the normal striatin gene, positive heterozygous if they only had 1 copy of the mutated striatin gene, or positive homozygous if they had 2 copies of the mutated gene. Echocardiograms were performed by a board-certified cardiologist or a resident under the supervision of a board-certified cardiologist. End-diastolic and end-systolic measurements of left ventricular (LV) size and ejection fraction were assessed on the right parasternal long-axis 4-chamber view using Simpson's method of discs.[29] The 12-lead ECG was performed with the dog in right lateral recumbency; the precordial leads (V_1-V_6) were placed according to the modified Wilson system except for V_1, which was placed at the costochondral junction of the right first intercostal space.[30] Recorded variables of interest on Holter monitoring included: percent ventricular ectopy (%VE); number of single VPCs, ventricular couplets, and runs of VT (per hour) and maximum rate of VT runs (beats per minute). Values between 0 and 1 were classified as <1 per hour.

2.2 | Electroanatomic mapping and RFCA

The mapping and ablation procedures were performed at the Translational Cardiac Electrophysiology Laboratory at the University of Pennsylvania Perelman School of Medicine by a translational cardiac electrophysiologist (CMT). Antiarrhythmic drugs (AADs) were discontinued for 5 half-lives before the procedure in all but 2 dogs. Opioids (butorphanol, fentanyl, or remifentanil) were administered as premedication in the first 3 cases, but avoided in the last 2 cases to minimize suppression of spontaneous VT. General anesthesia was induced with propofol (titrated to effect) and

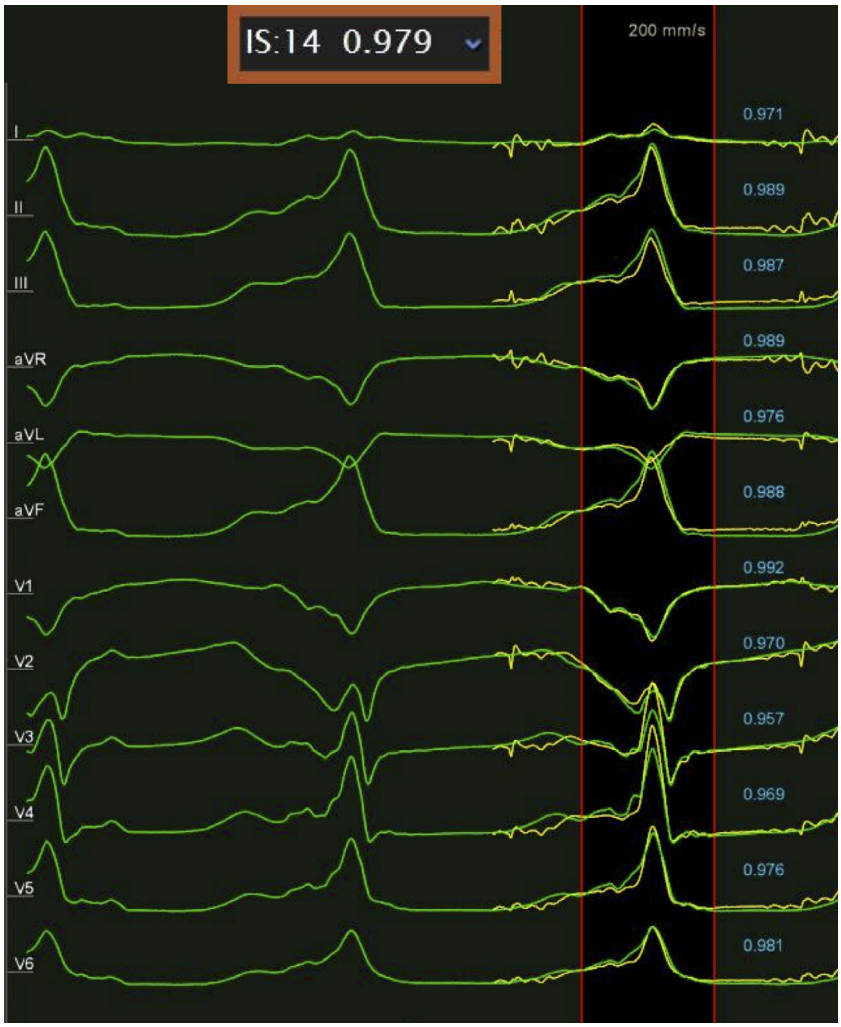

FIGURE 1 Pace mapping of ventricular tachycardia in a Boxer using the PASO module on the CARTO system. The native rhythm (green) is shown on a 12-lead surface ECG at 200 mm/s, and consists of ventricular tachycardia with a left bundle branch block morphology and inferior axis. The paced rhythm (yellow) is superimposed onto the native rhythm starting at the third complex and the PASO module calculated the correlation between paced and native QRS morphologies in each lead. For example, in lead I, the correlation is 0.971, or 97.1%. An overall correlation percentage is shown at the top of the figure, illustrating 0.979 or 97.9% concordance at this paced location. Radiofrequency catheter ablation was subsequently performed at this site

midazolam (0.2 mg/kg), and maintained with isoflurane (1%-2%) and oxygen supplementation. In the last 2 dogs, epidural anesthesia[31] was administered to provide analgesia while decreasing the amount of isoflurane required. With dogs in dorsal recumbency, the CARTO 3 EAM system (Biosense Webster, Diamond Bar, California) was set up using a location magnet placed below the operating table and 6 CARTO patches placed around the thorax to provide fixed reference points. Dogs were fitted with a grounding pad placed on the caudal dorsum, defibrillation patches on either side of the thorax over the palpable apex beat, and 12-lead ECG patches.

Femoral venous vascular sheath placement was achieved percutaneously in 4 dogs and via surgical cutdown in 1 dog. Femoral arterial access was achieved percutaneously in 2 dogs, via cutdown in 2 dogs, and not performed in 1 dog. Two dogs underwent intraprocedural anticoagulation using IV heparin (2000 IU [85 IU/kg] in the first and 7000 IU [213 IU/kg] in the second case). A specialized catheter to perform intracardiac echocardiography (CARTO Sound 8F SOUNDSTAR, Biosense Webster, Diamond Bar, California) was advanced into the right atrium. Two-dimensional images traced in multiple imaging planes facilitated 3D reconstruction of both ventricles. Although not a requirement for EAM and RFCA, this modality can aid in the rapid creation of a 3D shell of the heart chambers and provides monitoring of global myocardial function during the procedure. A bidirectional mapping and ablation catheter (ThermoCool SmartTouch Surround Flow, Biosense Webster, Diamond Bar, California) was advanced into the RV. If VT did not occur spontaneously, programmed electrical stimulation (PES) was performed to induce VT, starting at the RV apex using a current strength twice the capture threshold and a pulse width of 2 ms. Trains of 8 S1 extrastimuli followed by progressively premature S2 to S5 extrastimuli at cycle lengths from 400 to 170 ms were delivered. If indicated, PES was repeated from the right ventricular outflow tract (RVOT), LV apex or both. Isoproterenol (0.0005-0.15 μg/kg/min) was also administered in some cases to enhance VT inducibility. If the induced VT was not hemodynamically tolerated, it was terminated by ventricular overdrive pacing or electrical cardioversion. In some cases, VT induction was not attempted if frequent spontaneous VPCs were present because induced VT often was not hemodynamically tolerated and we had concern that induced VT may not consistently reflect clinically relevant, spontaneously occurring VT.

Several different mapping techniques were employed, including: (a) substrate/voltage mapping, (b) activation mapping, (c) entrainment

mapping, and (d) pace mapping. Mapping of the LV also was performed, except in 2 cases. During voltage mapping, areas of low voltage and fractionated electrogram (EGM) signals were interpreted as abnormal or scar tissue; abnormal bipolar voltage was defined using conventional cutoff values (low bipolar voltage ≤1.5 mV and very low bipolar voltage ≤0.5 mV).[32] Adequate catheter contact, measured via force applied at the catheter tip, was essential to confirm that low-voltage areas were not a result of inadequate catheter-tissue contact.[33] Unipolar endocardial voltage recordings also were recorded to facilitate identification of potential transmural or epicardial scar tissue (normal RV > 5.5 mV, LV > 8.27 mV).[28,32,34] Activation mapping utilizes the local activation time (time from appearance of an intracardiac EGM compared to a reference time point, such as the peak of the R wave on the surface ECG) to identify sites of earliest activation and to construct the depolarization sequence of hemodynamically stable VA. A focal mechanism is identified when a wave front spreads centrifugally from a single site of earliest activation. A reentrant mechanism occurs when a unidirectional wave front that encompasses the full range of mapped activation times returns to the site of earliest activation. When hemodynamically tolerated, entrainment mapping, via continuous ventricular pacing at a shorter cycle duration than the ongoing VT, was used to identify different components of a reentrant circuit. For example, the central isthmus is defined when a site of mid-diastolic potential demonstrates concealed fusion, an after pacing interval comparable to the total cycle duration (ie, a difference <30 ms), and a stimulus-to-QRS time that is 30% to 50% of the total cycle duration.[35] Pace mapping involved identifying sites at which a paced beat created a QRS complex morphology that showed >95% concordance to those seen during spontaneous VA, as calculated by the PASO module on CARTO 3 (Figure 1).[36] These sites were considered closest to an automatic focus or exit site of a reentrant circuit. A reentrant mechanism additionally is considered when there is reproducible initiation of VT with extrastimuli, entrainment from remote sites demonstrates fixed and progressive fusion, or other criteria as described elsewhere.[37]

Target sites for RFCA were selected as: (a) the earliest activation site in a focally activated arrhythmia, (b) the isthmus site of a reentrant circuit identified from entrainment mapping, or (c) the highest congruent site from pace mapping. Irrigated RFCA was delivered with a power of 20 to 35 W, maximum duration of 60 seconds, and a target contact force >10 g. Radiofrequency catheter ablation was considered successful intraoperatively when (a) VT was terminated during the ablation and could not be re-induced using the previously performed PES protocol, or (b) VA did not recur over 30 minutes, including during pharmacologic challenge with isoproterenol. Recorded data included number of VPC morphologies, inducibility of VT (yes/no), anatomic regions of the heart that demonstrated low-voltage areas, low-voltage endocardial surface area (in cm^2 and percent of total endocardial surface area), number of RFCA lesions delivered, and anatomic regions where RFCA was performed. The anatomic regions were classified according to standardized nomenlature for RV and LV segments.[38-40] At the end of each procedure, vascular sheaths were removed. Firm pressure was applied to the venous access sites for 30 minutes except in 1 case in which the vein was ligated. Arterial access sites were ligated except in 1 case of percutaneous arterial access, in which firm pressure was applied.

TABLE 1 Demographic, clinical, and electroanatomic findings in Boxers undergoing radiofrequency catheter ablation

	All dogs (n = 5)
Age at time of initial diagnosis (years)	4.8 (1.2-8.9)
Age at time of procedure (years)	8.5 (4.9-10.3)
Sex (M/F)	2/3
Weight (kg)	30 (22-32.8)
Number with negative striatin genotype/positive heterozygous/positive homozygous[a]	2/1/1
LV EDV (mL/kg)	2.62 (1.52-2.95)
LV ESV (mL/kg)	1.15 (0.67-1.60)
EF (%)	55.6 (45.6-57.3)
Number of VPC morphologies per dog	
On initial ECG	2 (1-3)
During EAM	2 (1-3)
Sustained VT on induction (yes/no)	3/2
Bipolar RV low-voltage (≤1.5 mV) area (cm^2)	0 (0-10.8)
Bipolar RV low-voltage (≤1.5 mV) area (%)	0 (0-8.4)
Bipolar LV low-voltage (≤1.5 mV) area (cm^2)[b]	0 (0-0)
Bipolar LV low-voltage (≤1.5 mV) area (%)[b]	0 (0-0)
Number of RFCA sites per dog	18 (3-43)
Holter monitor parameters before RFCA	
Ventricular ectopy (%)	8.6 (0.5-10)
Single VPCs (# per hour)	69 (12-249)
Ventricular couplets (# per hour)	2 (0-16)
VT runs (# per hour)	5 (<1-46)
Holter monitor parameters after RFCA	
Ventricular ectopy (%)	2.8 (<0.1-20.8)
Single VPCs (# per hour)	101 (<1-334)
Ventricular couplets (# per hour)	3 (0-6)
VT runs (# per hour)	0 (0-2)
Alive (yes/no)	2/3
Time to last follow-up (days)	312 (33-773)

Notes: Values are displayed as median (range). Time to last follow-up is reported as number of days from EAM/RFCA to death/euthanasia or time of writing.

Abbreviations: EAM, electroanatomic mapping; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; F, female; LV, left ventricle; M, male; RFCA, radiofrequency catheter ablation; RV, right ventricle; VPC, ventricular premature complex; VT, ventricular tachycardia.

[a]Striatin result was not available for 1 dog.

[b]Data were only available in 3 dogs.

2.3 | Follow-up

Each dog was monitored in the intensive care unit for at least 16 hours after the procedure. One to 2 months after RFCA, Holter monitoring was repeated to reassess VA.

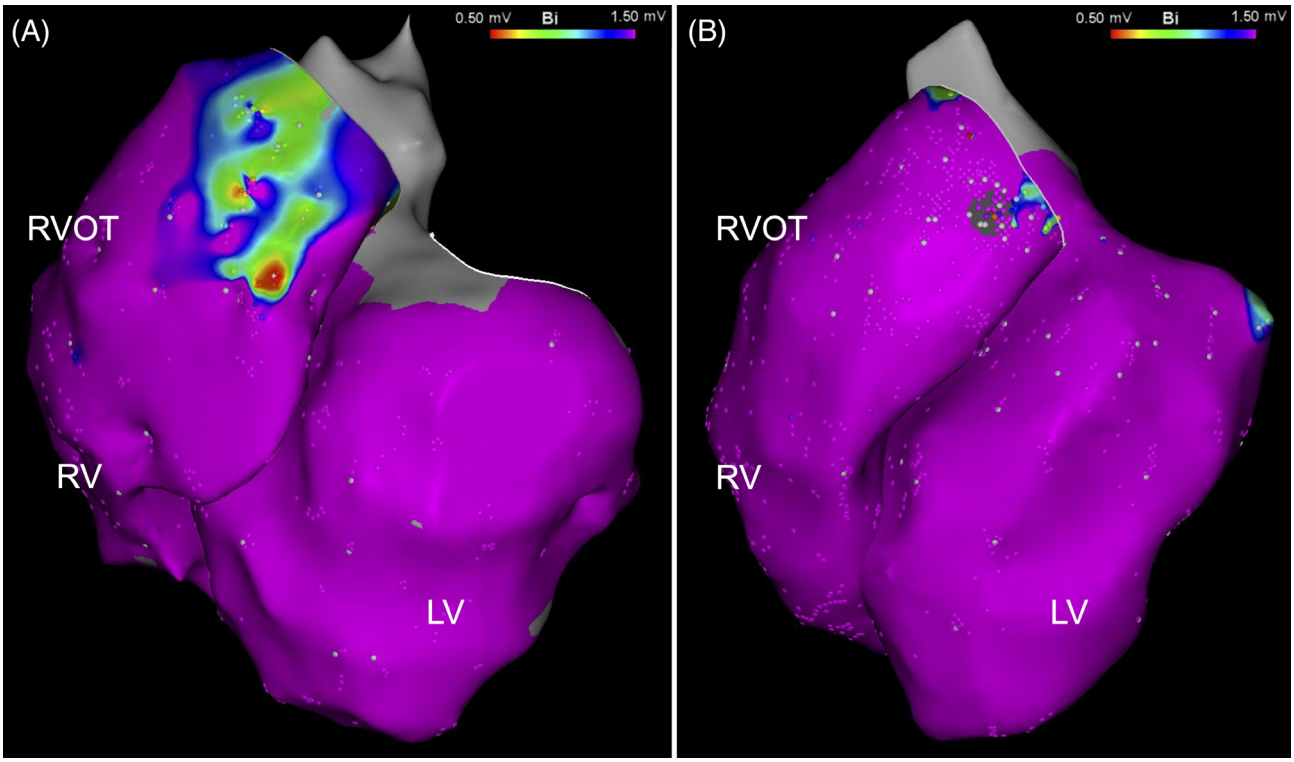

FIGURE 2 Bipolar voltage mapping of the right ventricle (RV) and the left ventricle (LV) in 2 Boxers during sinus rhythm. The voltage signals of intracardiac EGMs are displayed in the RV and LV. Red represents voltages that are ≤0.5 mV and purple represents voltages that are ≥1.5 mV. Intermediate ranges are represented on a color scale as displayed in the top left corner of the figures. Regions with voltages <1.5 mV are consistent with electroanatomic scar, whereas regions with voltages >1.5 mV are consistent with normal conducting myocardium. The voltage mapping density was sufficient to allow detailed endocardial surface geometric reconstruction with a fill threshold ≤10 mm. A, This Boxer had evidence of electroanatomic scar at the endocardial surface of the right ventricular outflow tract (RVOT). B, This Boxer had no evidence of electroanatomic scar; the minor color changes represent ablation sites and perivalvular structures. Bi, bipolar

2.4 | Statistical analysis

Descriptive analyses were performed; continuous variables were expressed as median (and ranges). Because 3 Holter monitors had a duration <48 hours, Holter variables were expressed either as %VE or as the number of beats or runs per hour for equivalent comparisons.

3 | RESULTS

3.1 | Clinical summary

Table 1 summarizes the demographic and clinical data. Individual data and antiarrhythmic drug treatments are presented in Tables S1 and S2, respectively. One dog was previously diagnosed with hypothyroidism, which was medically controlled. All 5 dogs initially were treated with sotalol after diagnosis of VT. Although 1 dog was maintained on the initial sotalol dose, the remaining dogs had 1 to 8 adjustments in antiarrhythmic drug protocols before EAM, either in dose, drugs used or both. One dog developed gastrointestinal upset after combining mexiletine with sotalol. Two dogs had persistent collapse episodes despite treatment adjustments.

On 12-lead ECG, the median number of VPC morphologies identified per dog was 2 (range, 1-3). Two dogs had both LBBB and right bundle branch block (RBBB) morphologies, 1 dog had only RBBB morphology, and 2 dogs had only LBBB morphology. Holter monitoring was performed 13 to 105 days before EAM (median, 27 days). Median percentage of VE was 8.6% (range, 0.5%-10%), number of single VPCs was 69 per hour (range, 12-249 per hour), number of ventricular couplets was 2 per hour (range, 0-16 per hour), and number of VT runs was 5 per hour (range, <1-46 per hour). Individual Holter data are presented in Table S2.

Antiarrhythmic medications were suspended in all but 2 dogs before EAM; no dog experienced any syncopal event during this brief washout period. The owner of the first dog enrolled in the study was uncomfortable stopping the antiarrhythmic medication after having witnessed a syncopal event in her dog before starting drug treatment. We thus aimed to target VT that was nonresponsive to medical treatment, but no VT could be induced during the procedure. Another dog experienced cardiac arrest at our hospital 2 weeks before while still taking antiarrhythmic medications. This dog had an exceptionally high VT burden, frequent syncopal episodes, and perceived high risk of sudden death. Although antiarrhythmic medications were not suspended, this dog still had VT the morning of and throughout the procedure.

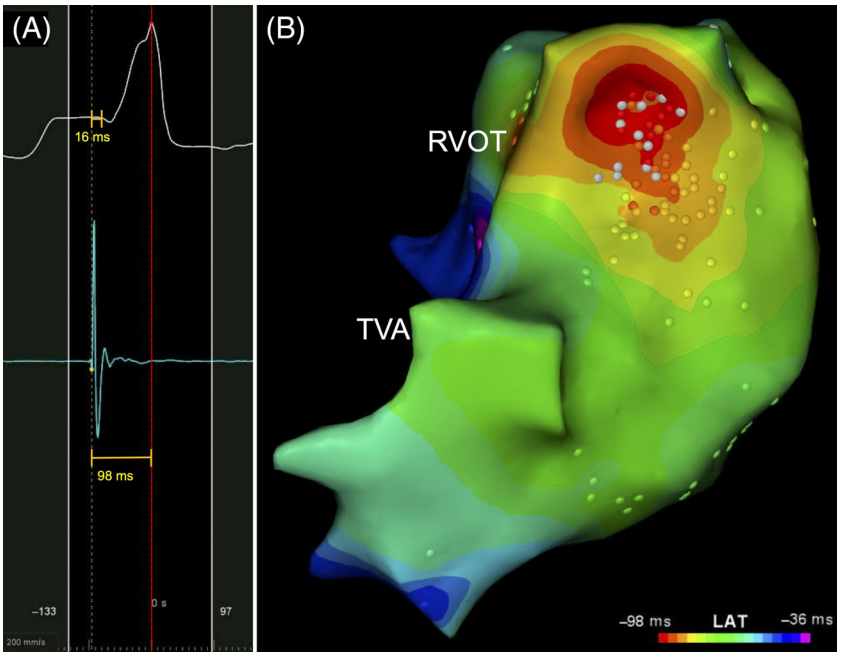

FIGURE 3 Activation mapping of a ventricular premature complex (VPC) in a Boxer with a focal activation pattern. A, The surface ECG appearance of a VPC is shown at the top (white trace) at 200 mm/s, and an intracardiac electrogram (EGM) of the same VPC at the septal aspect of the right ventricular outflow tract (RVOT) is shown below (blue trace). The vertical yellow dotted line marks the earliest appearance of the EGM, whereas the vertical red line marks a reference time (time 0 s) at the peak of the R wave on the surface ECG. The intracardiac EGM occurs 16 ms before the onset of the QRS complex in the surface ECG and approximately 98 ms before the reference time, demonstrating that the location of the mapping catheter is at or near the site of earliest activation. B, An isochronal map is shown in the right ventricle, demonstrating centrifugal activation of the same VPC from a focal site at the septal RVOT. Each individual point signifies the earliest activation time of a local EGM, represented by a color that covers an area up to 15 mm away. These local activation times (LATs) are signified by layers of different colors, with the earliest activation (−98 ms) represented in red and the latest activation (−36 ms) represented in purple. The full extent of the VPC in the right ventricle was not fully mapped, contributing to the irregular shape of the ventricle. LAT, local activation time; TVA, tricuspid valve annulus

3.2 | Electroanatomic mapping and RFCA findings

The median number of VPC morphologies observed during EAM was 2 (range, 1-3). Sustained VT was induced in 3 dogs, although aggressive PES was often necessary (ie, multiple extrastimuli at short cycle lengths). One dog had frequent spontaneous VPCs where activation mapping was used as the sole method for identifying target ablation sites, and VT induction with PES was not pursued. Only 1 dog had noninducible VT, which was the aforementioned first dog that was maintained on antiarrhythmic medications throughout the procedure (but single spontaneous VPCs were intermittently observed).

Bipolar and unipolar voltage mapping was successfully performed in the RV of all dogs (Figure 2). Three dogs had no low-voltage areas. In the remaining 2 dogs, the median low-voltage area was 10.8 cm^2 (range, 10.7-10.8 cm^2) and 8.0% (range, 7.2%-8.4%) respectively, of the endocardial surface area. These areas were located in the RVOT and cranial RV. Unipoloar voltage maps were also normal in areas of normal bipolar voltage maps. Left ventricular voltage mapping was performed in 3 dogs, but no low-voltage areas were identified.

Activation and entrainment mapping could not be performed in all cases, and thus the underlying arrhythmogenic mechanism can be speculated upon in only a few dogs. In dog 1, only rare spontaneous VPCs occurred during the procedure and VT was not inducible; the target ablation site thus was identified solely using pace mapping. Reentry was confirmed in dog 2 because of the presence of progressive fusion, but further activation or entrainment mapping could not be pursued because of poor hemodynamic tolerability of VT. Similarly, additional mapping could not be performed in dog 3 because of hemodynamic instability during VT. Activation mapping was performed successfully in dogs 4 and 5, and identified a focal arrhythmia mechanism (Figure 3; Video S1). However, entrainment mapping was not feasible in these dogs because of the lack of sustained VT.

The median number of RFCA lesions delivered was 18 (range, 3-43). The RFCA lesions were delivered to the RVOT (Video S2), cranial portion of the RV free wall, right aortic valve cusp, and the basilar cranial LV near the mitral valve annulus. In 3 dogs, RFCA was concluded even though VT still could be induced after RFCA. Ventricular fibrillation occurred in 2 dogs during RFCA. After defibrillation, 1 of these dogs developed asystole followed by pulseless electrical activity, which warranted cardiopulmonary resuscitation. Although return of spontaneous circulation was achieved, recovery of the dog was prioritized and no further VT induction or RFCA were performed. In the remaining 2 dogs, VT only could be induced with very aggressive PES protocols. Given the large number of lesions (18 and 43) delivered in these 2 dogs, the duration of the ablation procedure, and the possibility that the VT induced by these aggressive protocols may not reflect

clinical VT, further RFCA was not pursued. There was also concern that high numbers of RFCA might promote proarrhythmia.

3.3 | Follow-up and complications

The median number of days to discharge was 1 (range, 1-4); the dogs that had longer hospital stays experienced major hemorrhages (see below). Re-evaluation of Holter monitoring was performed 14 to 34 days (median, 23 days) after EAM and RFCA. The %VE and number of single VPCs increased in 3 dogs and decreased in 2 dogs, 1 of which had near resolution of all VA. However, all dogs had decreased runs of VT, with 3 dogs having resolution of VT. Median percentage of VE was 2.8% (range, 0.1%-20.8%), number of single VPCs per hour was 101 (range, <1-334), number of ventricular couplets was 3 per hour (range, 0-6), and number of VT runs was 0 per hour (range, 0-2; Table 1). Individual re-evaluation of Holter data is presented in Table S2. All dogs no longer collapsed after RFCA. Median follow-up time of all dogs was 312 days (33-773 days; Table 1). Two dogs were still alive at the time of writing. Of the 3 dogs that did not survive, 2 experienced sudden death (33 and 377 days after RFCA) and the third was euthanized because of progressive hind limb weakness and decreased quality of life. Individual follow-up data are presented in Table S1.

Procedural complications included bruising at the vascular access site (n = 3), ventricular fibrillation (n = 2) or persistent VT (n = 1) necessitating defibrillation or cardioversion, and retroperitoneal hemorrhage (n = 1). Postoperative complications included arterial access site hemorrhage (n = 1), new onset of supraventricular tachycardia (n = 1), persistent right pelvic limb weight-bearing lameness, and hind limb weakness (n = 1). No dogs died during or immediately after the procedure.

4 | DISCUSSION

We evaluated the ability of EAM to help guide RFCA in Boxer dogs with symptomatic VT or persistent VT despite antiarrhythmic treatment. In our study, EAM identified abnormal voltage maps in 2 dogs. The distribution of low-voltage areas was similar to both electroanatomic and histopathological findings in people, where fibrofatty infiltration predominantly extends from the tricuspid or pulmonic valve or both to the RV free wall but sparing the RV apex.[6,26,34] Previous histopathological studies in Boxers also have shown that fatty tissue replacement occurred most substantially in the RV free wall and RVOT.[4] Additionally, 1 dog's VA appeared to originate from the LV free wall. Involvement of LV is more frequent than previously thought in people with ARVC, and Boxer dogs also have documented evidence of LV histopathological changes.[4,26,34,41,42] These parallels reinforce the value of the Boxer to serve as a spontaneous animal model of arrhythmogenic cardiomyopathy.

On the other hand, EAM showed that 3 dogs had normal voltage maps without electroanatomic scar. This finding was unexpected given that ARVC is classically characterized by fatty or fibrofatty infiltration causing scar-related VT.[26,34,43] Because reference values for myocardial voltage amplitudes in dogs are scarce, it is possible that early or low-grade endocardial changes were missed. However, we applied stringent voltage cut-offs to classify normal, as compared to the literature.[28,32] It is also possible that their electroanatomic scar instead had a more epicardial distribution. In early stages of ARVC in people, scar and reentry circuits are located nearly exclusively in the epicardium; it is not until more advanced stages of disease that the VT substrate reaches the endocardium.[44] Although direct epicardial mapping was not performed in our study, a recent investigation in human ARVC patients determined that detection of isolated epicardial substrate may be suggested by endocardial unipolar voltage abnormalities.[45] Specifically, areas with abnormal endocardial unipolar EGMs corresponded to abnormal epicardial bipolar voltage maps and VT circuits isolated to the epicardium, demonstrating the utility of unipolar voltage assessment as a valuable surrogate to interrogate the epicardium without direct access. Although unipolar threshold values have not been established specifically in Boxers, we utilized more conservative lower thresholds than did previous studies in dogs,[28] and infer that it is unlikely that the dogs in our study with normal bipolar endocardial substrate had confluent unipolar abnormalities suggestive of an epicardial scar. This observation does not eliminate epicardial origin of arrhythmia, nor replace epicardial methods of arrhythmia interrogation, such as activation mapping and entrainment mapping, which were not pursued in our study.

Alternatively, it is possible that VAs exist in Boxers even in the absence of scar, because some humans with sudden death and ARVC genotypes also lack scar or histological abnormalities.[46] Indeed, translational research of human and murine ARVC suggests a continuum between electrical and structural disease phases, raising the possibility of different underlying arrhythmia mechanisms, depending on the stage of disease.[47] Finally, other disease processes may mimic ARVC.[48] For example, a differential diagnosis for ARVC in people is idiopathic outflow tract ventricular tachycardia (OTVT), because both are characterized by VA with a LBBB pattern.[6,49,50] In contrast to ARVC, OTVT is nonfamilial and characterized by the absence of histopathological abnormalities.[50,51] Mechanistically, OTVT is a result of triggered activity (delayed afterdepolarizations) and is usually adrenergically mediated.[50] Further histopathological study is warranted to validate the electroanatomic findings and investigate possible causes of VT in dogs with or without endocardial scar.

Given our small study population and evolving methodology, representative success rates and long-term outcomes of RFCA could not be determined. Since the first demonstration in 1989, the acute success rates of endocardial ablation in eliminating VT in human ARVC patients have been 60% to 80%, although long-term success rates at a follow-up of 3 to 5 years are less at 50% to 70%.[16,27,52] All dogs in our study showed decreased runs of VT with resolution of VT runs in 3 dogs. As number of VT runs was the only variable associated with a significant risk of death in a retrospective study of Boxers with ARVC,[15] this outcome may represent a clinically relevant goal for this patient population. However, 3 dogs had persistent or increased numbers of single VPCs, whereas 2 dogs had decreased numbers of single

VPCs, with only 1 dog experiencing near resolution of all VA. This finding remains concerning because a recent study in humans with ARVC found that life-threatening VA or sudden cardiac death can be predicted based on VPC count.[53] In addition to daily variation, the lack of consistent VPC reduction may be influenced by several factors. First, the progressive nature of fibrofatty infiltration may favor the development of new reentry circuits or arrhythmogenic foci that will manifest additional VE.[27] Second, additional arrhythmogenic foci near the epicardium may have been missed without a direct epicardial mapping approach. However, considering the novelty of this procedure in dogs, we were concerned by the additional challenge of pericardial access in the absence of pericardial effusion and possible complications, including intrapericardial bleeding from RV puncture or pericarditis.[54] Third, overaggressive RFCA and PES could have had a counterproductive effect. Radiofrequency catheter ablation may have a proarrhythmic effect,[55] which has been identified in research beagle dogs undergoing electrical catheter ablation.[56] Furthermore, aggressive PES may induce VT morphologies that are clinically irrelevant.[57] Finally, optimal protocols to induce and maintain clinically relevant, but hemodynamically tolerated VT for analysis (and thus identification of ideal RFCA sites), remain to be investigated.

Not only is sustained and hemodynamically tolerated VT desirable for identifying critical components of arrhythmogenesis, but the ability to initiate VT and then demonstrate noninducibility is also fundamental to assessing intraprocedural RFCA success.[57] Sustained VT was inducible in dogs with electroanatomic scar, likely because these dogs had scar-related reentrant VT, and reproducible initiation of VT is a feature of reentry.[58] However, sustained VT was difficult to induce in the dogs without electroanatomic scar, even with pharmacological challenge. Aside from the underlying electroanatomic substrate, inducibility of VT can be influenced by drugs and autonomic state.[57] The first dog in our study was continued on sotalol throughout the procedure and received opioids for premedication, and was found to have noninducibile VT. In people and earlier veterinary studies, antiarrhythmic medications were discontinued 5 half-lives before the procedures.[20,22,23,59] Opioids can increase vagal tone, and inhalant anesthetics such as isoflurane can prolong action potential duration, delay atrial and ventricular repolarization, and decrease tachyarrhythmia inducibility in vitro.[59] Furthermore, most of the episodes of induced VT were not hemodynamically tolerated, which is likely related to the general depressant effect of anesthesia.[60] As such, we have found that suspending antiarrhythmic medications, avoiding perioperative opioid drugs, and minimizing inhalant anesthetics by using epidural analgesics may minimize the depressant factors affecting VT inducibility and hemodynamic stability.

In people, adverse events from endocardial ablation include hemodynamic instability and death, pericardial effusion and cardiac tamponade secondary to myocardial perforation, thromboembolic events, conduction system damage (eg, atrioventricular block necessitating permanent pacemaker placement), and vascular access complications, including femoral pseudoaneurysms, femoral arteriovenous fistula, and groin hematoma.[61,62] Ventricular fibrillation occurred in 2 dogs. One dog required resuscitative efforts (and successfully recovered), whereas in the other dog VF was immediately electrically defibrillated with nosus interruptions to the procedure. Sustained VT and VF are anticipated consequences of pacing maneuvers in dogs with a predilection for VT, and usually can be terminated successfully in the electrophysiology laboratory setting, as a result of immediate intervention. In our study, several dogs developed bleeding complications including bruising, major and minor hemorrhage from arterial access sites, and retroperitoneal hemorrhage. Systemic intraprocedural anticoagulation is not routinely performed for RV mapping and ablation in people unless a prolonged procedure is anticipated or if the patient has risk factors for thromboembolism. On the other hand, left heart catheterization requires systemic intraprocedural anticoagulation to decrease the risk of thromboembolic events.[59] Most commonly, unfractionated heparin is administered as an initial bolus (5000-10 000 IU or 50-100 IU/kg) followed by intermittent boluses, continuous infusion or both to maintain a target activated clotting time (ACT) >250 to 350 seconds. In our first dog, heparin (85 IU/kg) was administered for RV mapping and may have contributed to bruising, although ACT was not measured for confirmation. In the second dog, heparin (213 IU/kg) was administered for LV mapping and may have contributed to retroperitoneal hemorrhage, although ACT was within the therapeutic range (260 seconds) intraoperatively and prothrombin time, partial thromboplastin time and thromboelastography were normal postoperatively. This same dog underwent cardiopulmonary resuscitation, and thus traumatic injury from chest compressions is also possible. Two other dogs experienced bleeding complications associated with arterial access but did not receive heparin. These findings may reflect inherent species differences regarding hemostasis. For example, thrombotic risk appears higher in people with atrial fibrillation compared to dogs.[63,64,65] Although comorbidities such as diabetes and chronic hypertension likely contribute to thrombosis in people, left ventricular dysfunction and left atrial enlargement are present in both species yet do not represent substrantial risk factors for dogs.[65,66] In addition, hemostasis in dogs may be affected by limited ability to restrict movement postoperatively. For these reasons, appropriate anticoagulation protocols in dogs may differ from those used in people. We currently no longer use prophylactic anticoagulation routinely for these procedures, but further study is warranted.

One dog in our study developed moderate aortic regurgitation and mild mitral regurgitation. In a large study of human patients undergoing retrograde aortic RFCA, the frequency of new valvar regurgitation was 1.9% and only mild regurgitation was induced.[67] In young human patients where the size of the catheter relative to aortic size is more comparable to dogs, the incidence of mitral regurgitation was higher at 25%, although no aortic regurgitation was induced.[68] In our dog, the aortic regurgitation may have been related to repeated prolapse of the catheter tip across the valve because of the small heart size. We now consider placing long introducer sheaths directly across the aortic valve to minimize such movements. This same dog also had progressive left-sided cardiac enlargement and new frequent episodes of supraventricular tachycardia. The cause of the latter was unknown, because no ablation lesions were delivered in the atria. The cardiac troponin I concentration was 0.84 ng/mL (reference range, <0.06 ng/mL) 2 months after the procedure. Resolving myocarditis is a possibility if we assume the troponin concentration was higher

earlier. Atrial involvement of ARVC or progressive atrial stretch from new valvular regurgitation also is possible cause.

Our pilot study has several limitations. Importantly, the number of dogs is small and these 5 cases represent the initial experiences in treating a disease characterized by a complex arrhythmogenic substrate. The mapping and ablation protocols and techniques thus have been modified throughout the study to improve efficacy and safety of the procedure, and will likely continue to evolve with more experience and understanding. Because of the small population size and mapping limitations (predominantly related to poor tolerability of VT), we can only speculate on the electrophysiological mechanism underlying the VT in a few dogs. Considering the wide spectrum of phenotypes, including presence and absence of scar, as well as different underlying electrophysiologic mechanisms of arrhythmias encountered in our study, further investigation into the origins of VA in Boxers in a larger patient cohort is necessary. Gross and histopathological assessments are not yet available to validate electroanatomic maps. Intraoperative anticoagulation protocols were not standardized and coagulation parameters were not rigorously monitored. Vascular access and hemostasis methods also were not standardized. Epicardial access was not pursued. Antiarrhythmic medications and timing of diagnostic tests were not standardized, and their effects on the results cannot be assessed. Another limitation is that the outcome measures were assessed using 48-hour Holter monitoring, 1 to 2 months after ablation. Arrhythmias are subject to substantial daily variation, and intermittent Holter monitoring may not accurately assess overall arrhythmic burden.[69] Furthermore, because of the presence of VA after RFCA in some cases, it was decided to continue and sometimes adjust AAD in those dogs after RFCA. This factor may have impacted the arrhythmia counts in follow-up Holter monitoring. However, the need for continued antiarrhythmic treatment after RFCA does not invalidate the possible benefits of this intervention for dogs with symptomatic VT. Up to 82% of human ARVC patients continue to take AAD after RFCA[70,71] because of residual VT. The success of VT ablation in humans is based on improvement of clinical signs and decreased arrhythmia burden and is not predicated on discontinuation of AAD.[72,73] Long-term clinical outcomes of RFCA in a large population of dogs will be important to evaluate its effects on survival, but was outside the scope of our study.

In conclusion, EAM and RCFA are feasible and can decrease the number of VT runs in Boxers with symptomatic VT. Boxers had variable electroanatomic and arrhythmogenic substrate, as well as right and left ventricular origin of VA. Larger, longitudinal studies are required to further elucidate arrhythmia mechanisms and long-term outcome after RFCA.

ACKNOWLEDGMENT

This study was funded by the American College of Veterinary Internal Medicine Resident Fund, the Companion Animal Research Fund, and the Winkelman Family Fund in Cardiovascular Research. We thank the owners whose dogs participated in our study and our colleagues in the PennVet cardiology department for recruitment and management of these patients. We thank Dr. Kate Meurs of the North Carolina State University Veterinary Cardiac Genetics Laboratory for generously offering striatin testing for our study. We thank members of the Translational Cardiac Electrophysiology Laboratory (Jonathan Salas, Christine Vaspoli, Loewe Kasprenski) for their assistance. We thank Dr. Frank Marchlisnki, MD, Director of the Cardiac Electrophysiology Program at the Hospital of the University of Pennsylvania for his continuous support and encouragement.

CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Approved by the IACUC, Office of Animal Welfare, University of Pennsylvania, protocol # 806634.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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How to cite this article: Crooks AV, Hsue W, Tschabrunn CM, Gelzer AR. Feasibility of electroanatomic mapping and radiofrequency catheter ablation in Boxer dogs with symptomatic ventricular tachycardia. *J Vet Intern Med*. 2022;36(3):886-896. doi:10.1111/jvim.16412