

Electrophysiology Testing in Drug Development: Evaluation of Intracardiac Conduction Parameters in Dogs

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1 INTRODUCTION

Atrial fibrillation (AF) affects about 3 million people in the US, 30% of who experience no symptoms at all. Atrial fibrillation is one example of a cardiac arrhythmia that can cause a disturbance in normal electrical conduction of the heart. Electrophysiology testing is routinely performed in human medicine through cardiac catheterization to assess arrhythmias, such as AF, and identify any sites within the conduction system for blocks or delays. Typically, this assessment is conducted for patients with existing arrhythmias, and this medically common practice is rarely performed during preclinical drug development. The value of the assessment during early drug development would be to identify a potential risk of generating an arrhythmia, particularly for compounds that target cardiac ion channels and later in development, for advanced compounds that identify with arrhythmia generation through electrocardiographic evaluation. Electrophysiology testing investigates an arrhythmia origin, identification of the site for conduction blocks or delays and evaluates the electrical conduction from atria to the ventricles. The specialized cardiac catheters are placed to allow for the collection of conduction times between different portions of the heart. Being able to further investigate rhythm disturbances may provide useful information when the ECG from animals with telemetry units does not provide this level of investigation. The objective of this study was to evaluate the cardiac conduction times and effective refractory periods (ERP) from the sinus node through to the ventricles in male beagle dogs.

2 MATERIALS AND METHODS

All procedures conducted were approved by the Charles River Institutional Animal Care and Use Committee (CRL Ashland, Ohio). Four male beagle dogs (Marshall BioResources) weighing between 10 and 12 kilograms were used. Dogs were pre anesthetized with Propofol (4-10 mg/kg IV) and intubated for maintenance of anesthesia with inhaled Isoflurane (1-5%). Bupivacaine was used on incision sites.

Limb lead ECG electrodes were placed on the chest in a modified lead II configuration. Vessel introducers were placed in the jugular and femoral veins, for placement of the pacing and biopotential cardiac catheters using either the Seldinger wire technique or blunt dissection. Multielectrode intracardiac catheters were advanced, under fluoroscopic guidance, through the vessel introducers. Two decapolar catheters were placed with one having the distal tip in the right ventricular apex (RVA) with the 5th and 6th electrode positions utilized for collection of the HIS bundle (HB) electrogram and another one with the distal tip positioned in the high right atrium (HRA) (Figure 1). A quadripolar catheter was placed in the coronary sinus (CS) measuring atrial conduction parameters (Figure 1). Additionally, a Millar pressure sensing catheter was placed in a femoral artery. The intracardiac and Millar catheters were connected to emkaTECHNOLOGIES IOX2 data acquisition system.

Recordings were collected during the dog's intrinsic heart rate: HRA to left atrium P or A wave (PA) from the CS, A to H (AH) and H to V (HV) intervals from the HIS bundle (Figure 2).

In addition to the same parameters collected above, the sinus node recovery time (SNRT) was assessed by implementing continuous 30 second atrial pacing at a 400, 330, and 300 ms cycle lengths. SNRT was defined as the time interval between the delivery of the last atrial stimulus and the first spontaneous atrial depolarization. Pacing was conducted through the distal electrode of the high right atrium catheter at a diastolic threshold of 2 mV and measurements were conducted in triplicate.

Sinus node corrected recovery time (SNCRT) was determined as the difference between SNRT and the intrinsic spontaneous cycle length (mean of five consecutive cycle lengths). The stimulus protocol for pacing S1 intervals were 400 ms (150 bpm), 330 ms (180 bpm), and 300 (200 bpm) in an 8 (S1) train + 1 (S2) approach with 8 impulses at the paced rhythms and a single (S2) premature impulse at progressively shorter coupling intervals (Figure 3a). The atrial effective refractory period (AERP) was assessed as the longest coupling interval (S1 to S1) of the premature atrial stimulus (S2), from the HRA pacing electrode, that did not result in a premature atrial depolarization (Figure 3b). Similarly, the atrioventricular nodal effective refractory period (AVNERP) was also assessed as the longest S1 to S2 interval, from the HRA pacing electrode, that did not result in a His bundle depolarization. Finally, the ventricular effective refractory period (VERP) was assessed as the longest S1 to S2 interval, from the RVA pacing electrode, that did not result in ventricular conduction (Table 1).

3 RESULTS

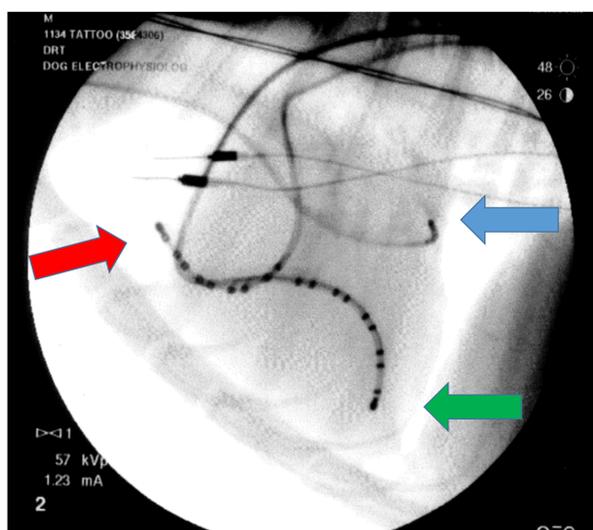


Figure 1. Radiograph demonstrating placement of intracardiac catheters. → High right atrium, → coronary ostium, → right ventricular apex.

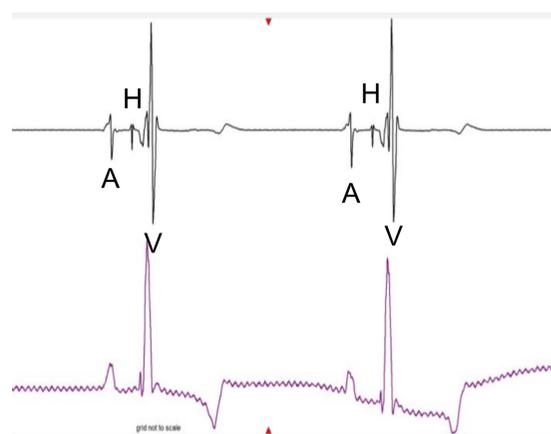


Figure 2. HIS bundle electrogram; A, H and V waves.

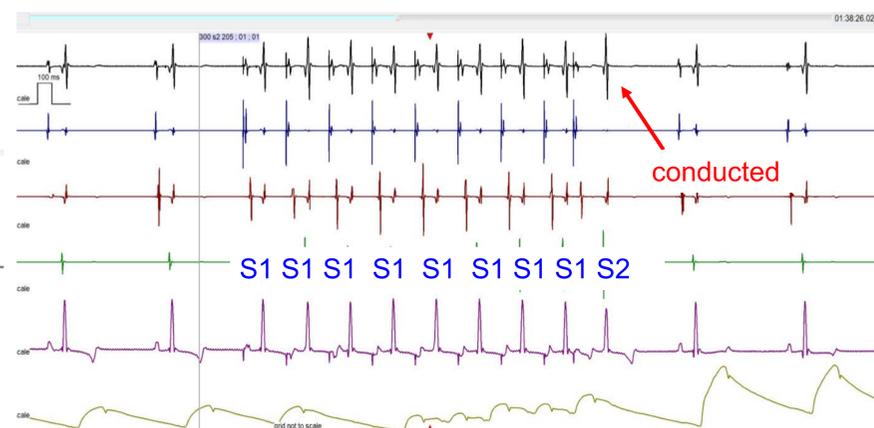


Figure 3a. Sinus and atrioventricular node refractory time assessment, S2 stimulus was conducted.

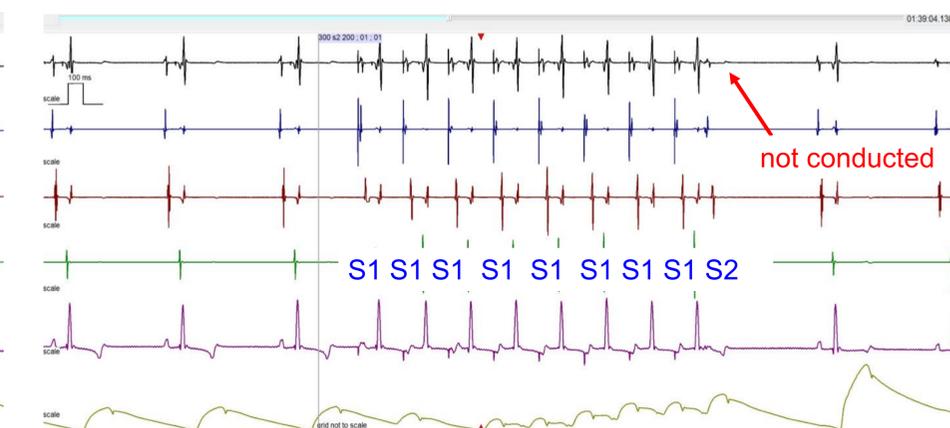


Figure 3b. Sinus and atrioventricular node refractory time assessment, shorter S2 stimulus was not conducted.

	Intracardiac Conduction Parameters (msec; mean ± SE)						
	SNRT	SNCRT	AERP	AVNERP	VERP	AH	HV
CL 400	790±284	172±122	220±84	220±84	155±10	55±6	38±19
CL 330	681±208	167±110	141±25	141±25	150±6	60±3	58±19
CL 300	639±161	126±65	153±26	153±26	150±5	50±4	52±21

Table 1. Intracardiac conduction parameters

4 DISCUSSION

Intracardiac placement of the electrode catheters and experience with conducting pacing studies are critical to the success of collecting intracardiac conduction times and effective refractory periods in dogs. The results of this study demonstrate both the comprehensive electrical evaluation of the heart and repeatability of the electrophysiology testing protocol for arrhythmia generation and for safety evaluation of new chemical and biological entities.