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Anodal Stimulation in Two Dogs with Transvenous Permanent Pacemakers

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Running head: Pacemaker anodal stimulation

Treatment of symptomatic bradyarrhythmias in the dog such as complete atrioventricular block often involves permanent implantation of a transvenous pacemaker. Both during and after implantation, the operator can telemetrically assess and adjust a variety of electrical parameters associated with the pacemaker function in order to optimize the sensitivity, reliability, and power consumption of the device. Herein we report an unexpected change in the paced electrocardiographic QRS complex morphology in 2 dogs undergoing bipolar pacing associated with changes in the pacemaker output amplitude settings during threshold testing. The exclusivity of the electrocardiographic changes solely on pacemaker output settings, consistency between the surface electrocardiogram and ventricular endocardial electrogram, and resolution of this phenomenon when dogs were re-programmed to unipolar pacing is consistent with depolarization of the ventricular myocardium by the anodal electrode of the pacing lead at high pacemaker amplitudes. Anodal stimulation is a potential cause of varying QRS complex morphology witnessed during pacemaker implantation and interrogation.

Two dogs that underwent permanent transvenous pacemaker implantation at the Ryan Veterinary Hospital of the University of Pennsylvania were suspected of experiencing anodal stimulation during pacemaker programming. Dog 1 was a 7 year old, 26 kg, male castrated English Bulldog with a history of exercise intolerance, intermittent poor appetite, and ascites. Physical examination of Dog 1 revealed a heart rate of 40 bpm with a regular rhythm and a distended abdomen. Dog 2 was a 7 year old, 45 kg, male castrated Shiloh shepherd with a history of 5 syncopal episodes during the previous 48 hours. Physical examination of Dog 2 revealed a heart rate of 40 bpm with a regular rhythm, a I/VI left-sided systolic murmur, intermittent isolated low intensity diastolic heart sounds, and occasional jugular vein pulses. Six-lead electrocardiogram (ECG) were performed in both dogs and revealed complete atrioventricular block. In dog 1, there was a ventricular escape rhythm at 40 bpm and an atrial P wave rate of 136 bpm. In dog 2, there was a ventricular escape rhythm at 35 bpm and an atrial P wave rate of 150 bpm. Echocardiography was performed in both dogs and revealed mild dilation of the left ventricle (normalized left ventricular end-diastolic dimension: dog 1, 1.8; dog 2, 1.7; 5-95% values of the reference range, 1.4-1.7) but no evidence of clinically significant myocardial or valvular cardiac disease. During the echocardiogram small volumes of pericardial and pleural fluid were detected in Dog 1. Along with the abdominal effusion that was previously detected on physical exam, these were thought to represent congestive heart failure as a result of the bradycardia. Abdominocentesis was performed and yielded 1380 mL of serosanguinous fluid. In Dog 2, the intermittent diastolic heart sounds and jugular pulses noted on physical examination in were assumed to represent a S4 (atrial contraction) heart sound and cannon ‘a’ wave resulting from atrial contraction against a close tricuspid valve, respectively. Placement of a permanent single-chamber transvenous ventricular paced, ventricular sensed, and inhibited (VVI) pacemaker was

performed in both dogs during the subsequent 12 hours. Pacemaker implantation was performed as previously described.[1] In both dogs, a 58-cm permanent endocardial pacing lead with active fixation[a] was introduced into the jugular vein and the helical lead tip was screwed into the endocardial surface of the right ventricular apex under fluoroscopic guidance. The opposite end of the lead was secured into the pacemaker generator[b] and successful capture of heart rhythm was confirmed by inspection of the surface ECG during the procedure. The pacemaker generators were secured in the subcutaneous tissues of the neck. Dogs were recovered and their ECGs were continuously monitored in the intensive care unit until discharge the following day. Pacing parameters at time of implantation in Dog 1 included the following: bipolar pacing and sensing; amplitude, 2.75 V; pulse width, 0.40 ms; sensitivity, 2.0 mV; lead impedance, 644 ohms; lower pacing rate, 90 bpm. Pacing parameters in Dog 2 included the following: bipolar pacing and sensing; amplitude, 3.30 V; pulse width, 0.34 ms; sensitivity, 2.0mV; lead impedance, 633 ohms, lower pacing rate, 75 bpm. Within 14 days after initial implant, both dogs underwent routine recheck and a ventricular strength duration threshold test was performed using a telemetric pacemaker interrogator[c]. The principles and practice of the strength duration threshold test have been previously described.[2] In brief, the test identifies safe and economic output settings by determining the lowest threshold at which the pacemaker discharge is able to generate cardiac depolarization. The test performs sequential reductions of the amplitude and pulse width of the pacemaker output until capture of the heart is no longer achieved. From these values, the pacemaker is programmed to an output setting with at least a 2x safety margin to ensure consistent capture of the heart, while avoiding unnecessarily high outputs that would deplete the battery life of the generator. In both dogs, the morphology of the paced QRS complexes on surface ECG was noted to suddenly change as the pacemaker amplitude was

reduced by 0.25 V increments during threshold testing. This phenomenon was further explored by recording standard 6-lead ECGs from each dog at two different amplitude settings. Dogs were placed in right lateral recumbency, and neither the position of the dogs nor placement of the limb electrodes on the dog's extremities was altered between the different recordings. In Dog 1 (Figure 1), the QRS complex morphology during pacing output amplitude of 2.75mV resembled a left bundle branch block-like morphology. The QRS complex in lead II was described as Rs with a notch in the R wave. The net polarity of the QRS complex was positive in leads I, II, III, and aVF, and negative in aVR. The mean electrical axis in the frontal plane using the method of vectors based on leads I and aVF was 66^0. When pacing amplitude was decreased to 1.0mV, the QRS complexes in leads II, III, and aVF abruptly became less positive, and the mean electrical axis shifted to 39^0. In Dog 2 (Figure 2A), the QRS complex morphology at a pacing rate of 75 bpm, pulse width of 0.4 ms, and bipolar pacing output of 6.0 V was a single tall R wave in lead II with positive QRS complexes in leads I, II, III, and aVF, and negative QRS complexes in leads aVL and aVR. The mean electrical axis was 82^0. When the pacing amplitude was decreased to 2.5 V, the QRS complex in leads II, III, and aVF abruptly became less positive, and the mean electrical axis shifted to 67^0.

Rule outs for the changes in paced QRS complex morphology included rate-dependent conduction abnormalities, dislodgement of the pacing lead from the endocardial surface, fusion beats, artifact associated with patient positioning or recording of the limb leads, or a change in the sequence of ventricular depolarization that was dependent on pacemaker output. Rate dependent conduction abnormalities were excluded due to the fact that the programmed rate settings were not changed. Intermittent dislodgement of the pacing tip from the endocardial

surface was deemed unlikely due the absence of intermittent failure to capture, normal lead impedance measurement and failure to witness the QRS complex morphology change in any other circumstance except when the pacing output was changed.

Fusion beats are the result of a simultaneous paced QRS complex and native ventricular escape beat, resulting in a QRS complex morphology that is a combination or fusion of the individual QRS complexes. In the current cases, fusion beats were unlikely due the consistency and rate of the altered QRS complexes when the programmed output was changed. To help rule out artifact associated with recording of the limb leads, a ventricular endocardial electrogram (VEGM) was recorded using the pacemaker interrogator at both the high and low pacing amplitudes (Figure 3). The VEGM is a recording of the ventricular electrical activity as measured from the right ventricular endocardial surface by the implanted endocardial pacing lead

We found that alterations in the pacing amplitude could induce an abrupt change in the QRS complex morphologies on both the VEGM and limb lead ECGs, which supported the notion that the change in QRS complex morphology was due to differences in the pattern of ventricular depolarization between the two different output settings. Rule outs for this phenomenon included a change in ventricular conduction secondary to high voltage emanating from the cathode tip or a change in ventricular conduction due to simultaneous capture of the heart from both the cathode and anode of the pacing lead. To further explore these possibilities, the pacemakers were programmed out of bipolar and into unipolar pacing mode and ECG recordings were performed in the unipolar pacing mode at both the low and high amplitudes (Fig. 2B). In contrast to what was seen during bipolar pacing, the QRS morphology during unipolar pacing did not change in relation to changes in output amplitude. This finding indicated that the altered sequence of ventricular depolarization was not due to high-energy impulses emanating solely

from the pacemaker lead's cathode tip. Based on the accumulated data, the cause of the altered QRS morphology associated with high bipolar pacing amplitudes was consistent with anodal stimulation of the ventricular myocardium.

Discussion

Artificial cardiac pacing is a common treatment for symptomatic bradycardia in the dog. The pacing system generates an electrical current across a circuit that simulates ventricular depolarization. The circuit is made up of two dipoles, one negative, the cathode, and one positive, the anode. In the bipolar pacing system both dipoles are located on the distal end of the lead (Figure 4A). In a bipolar lead with active fixation, the deployable helical screw serves as the cathode and is secured into the ventricular endocardium. A metal ring located several millimeters up the lead serves as the anode. During bipolar pacing, current exits the lead at the cathode and flows back to the anode. The directionality of the current results in depolarization of the myocardial tissue at the cathode tip, which triggers ventricular depolarization. For the circuit to be completed, the anode does not need to be specifically in contact with the myocardium so long as there is a route through blood or other tissue for the current to flow back to the anode. During unipolar pacing, the helical lead tip still serves as the cathode, but it is the pacemaker generator that serves as the pacing circuit anode. When the generator is placed within the subcutaneous pocket in the dog's cervical region, the circuit is completed and capture of the ventricular myocardium at the cathode tip can occur Of note, the directionality of current causes tissue in contact with the anode to become hyperpolarized, meaning it is farther away from the threshold for an action potential to develop,[3] and in both the unipolar and bipolar setting, the wave of ventricular depolarization originates from the cathode tip of the pacing lead (Fig. 4B).

Anodal stimulation describes circumstances when activation of the surrounding myocardium originates from a bipolar-programmed anodal pole. Anodal stimulation requires that the anode be very close to or in direct contact with the myocardium and that pulse amplitude is relatively high. In these instances, stimulation of ventricular myocardium can simultaneously originate from both the cathode and anode sites, thereby producing an alteration in the sequence of ventricular depolarization and change in the VEGM and ECG QRS complex morphology (Fig. 4C).

Anodal stimulation in human patients is an uncommon occurrence[4-8] . Similar to the situation in our two dogs, anodal stimulation in humans often is first suspected when the QRS complex morphology unexpectedly changes during threshold testing.[4] A diagnosis of anodal stimulation is largely one of the exclusions that rule out other causes such as patient movement, lead dislodgement, and equipment malfunction. In our two cases, these causes were deemed unlikely as previously described. The most convincing evidence of anodal stimulation was related to the findings during high output unipolar pacing. Switching to the unipolar pacing mode in our two dogs caused the pacemaker generator in the remote cervical site to assume anodal function, thereby precluding the possibility of ventricular anodal stimulation and preventing a change in QRS complex morphology during high outputs. Thus, these findings excluded the possibility that high output exclusively from the cathode could alter the sequence of ventricular activation, and supported a diagnosis of anodal stimulation.[4]

As previously mentioned, tissue in close proximity to the anode is hyperpolarized, and thus the ability of the anode to trigger an action potential seems paradoxical. A previous study[3] utilizing

epifluorescence imaging to measure transmembrane potential around anodal electrodes demonstrated that the hyperpolarized zone is shaped like a dumbbell, with a region of depolarized tissue within the convexity of the dumbbell (Figure 4D). It is from these "virtual cathodes" that anodal current is thought to originate.

The incidence of anodal stimulation in dogs undergoing artificial pacing is not known. In one report in human patients, [4] anodal stimulation could be purposefully and consistently produced in 52% of patients with bipolar pacing systems by temporarily stimulating at high output amplitudes. In dogs, anodal stimulation is likely under detected, especially if the voltage threshold for stimulation is above what most dogs are normally programmed to. In other instances, the change in QRS complex morphology indicating anodal stimulation might simply be overlooked or ignored. The likelihood of anodal stimulation increases not only with increasing output amplitudes but also with the closer proximity of the bipolar anodal ring to the ventricular myocardium. In dogs, standard practice positions the pacing lead deep within the right ventricular apex. This location might increase the likelihood of anodal stimulation due to the close proximity of the anodal ring to the surrounding myocardial tissue, especially in small dogs. In humans, anodal stimulation is more common in patients with an apically placed lead as opposed to one placed higher on the interventricular septum or right ventricular inflow tract.

Finally, other than being a potentially interesting phenomenon, are there any clinical consequences of anodal stimulation during bipolar pacing? Anodal stimulation should not be mistaken for intermittent lead dislodgement or equipment malfunction. Failure to recognize anodal stimulation might lead to unnecessary performance of radiographs, fluoroscopy,

ambulatory ECG monitoring, or lead replacement. In both humans[9, 10] and experimental dog models[6], anodal stimulation produces a shorter myocardial refractory period than cathodal stimulation and increases the risk of ventricular fibrillation. Thus, anodal stimulation should be avoided through careful attention to pacemaker output and pacing mode. However, in select circumstances, when cathodal stimulation fails to provide reliable capture, such as lead micro-dislodgement, right ventricular wall perforation, or development of fibrosis and exit block at the cathode tip, the anodal ring might still be in close enough proximity to the myocardium to provide palliative pacing and avoid the need to replace the pacing system. For example, Occhetta et. al.[5] reported perforation of a pacing lead through the right ventricular wall in an 86-yr-old human patient that resulted in failure to provide capture from the lead's helical cathode tip. Fortunately, the anode ring remained in contact with the myocardium, and by increasing the pacemaker output, reliable capture of the heart through anodal stimulation could be achieved. This particular patient was poorly suited to undergo lead replacement and chronic anodal stimulation was considered a reasonable long-term palliative solution. Another clinical consideration of anodal stimulation involves optimization of the single-lead pacing site or bi-ventricular or resynchronization pacing.[11, 12] Anodal stimulation can disrupt the planning or result of such efforts by pacing the myocardium from an unwanted site.[6, 8]

In summary, we report a change in paced QRS complex morphology in 2 dogs consistent with anodal stimulation. Anodal stimulation should be considered a rule out in cases where adjustment of the pacing output amplitude unexpectedly results in altered QRS complex morphology. Careful inspection of the ECG, VEGM, and comparison of QRS complex morphology during unipolar vs. bipolar pacing can help diagnose anodal stimulation. Anodal

stimulation might be a palliative alternative if cathodal stimulation fails to provide reliable capture.

Figures

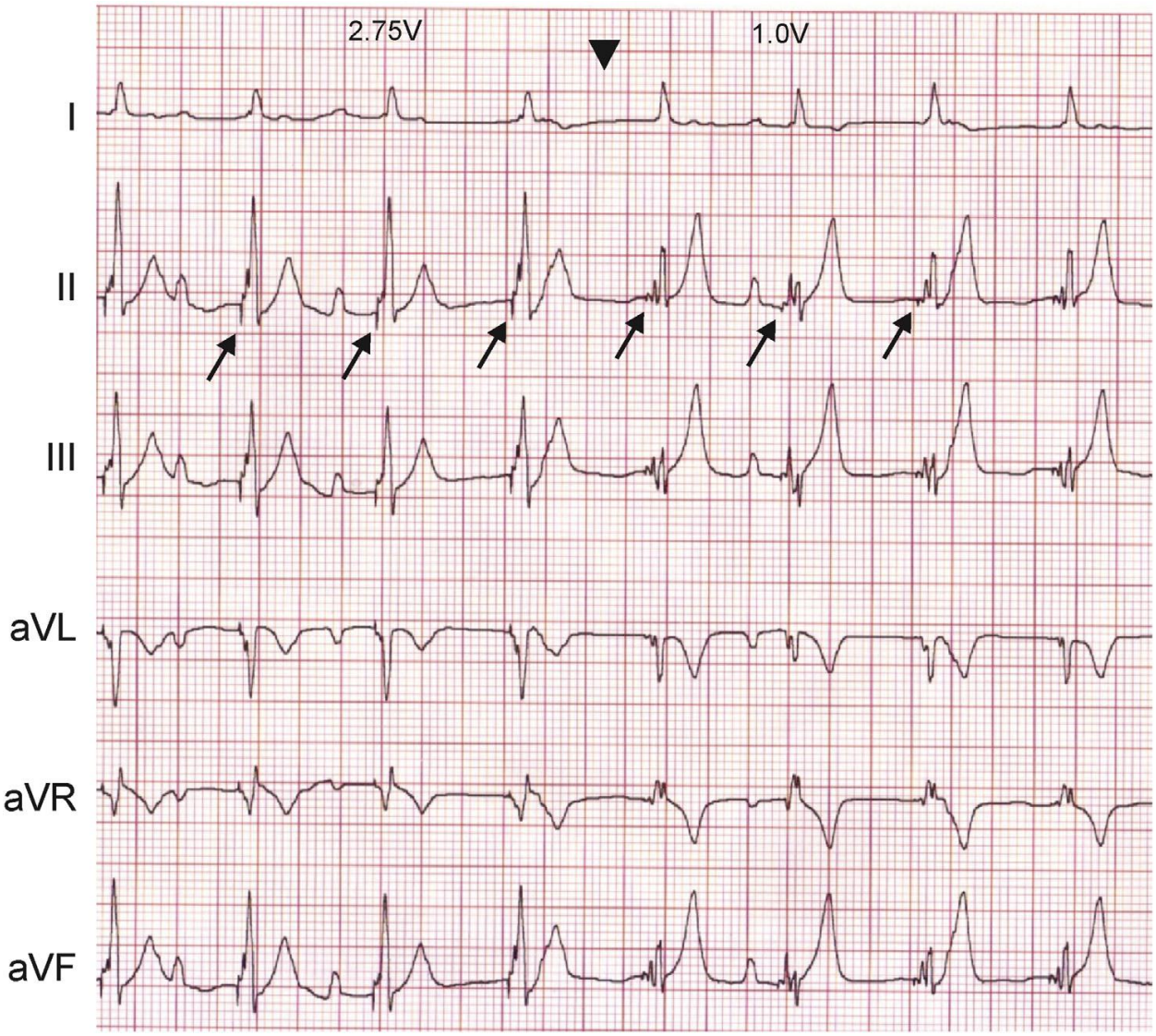

Figure 1. Six-lead ECG from Dog 1 demonstrating an acute change in the paced QRS complex morphology associated with a decrease of the paced output amplitude from 2.75mV to 1.0mV (arrowhead). The QRS complexes in leads II, III, and aVF become less positive, the QRS complex in lead I becomes more positive, and the QRS complex in lead aVL becomes less negative. See text for additional details. The arrows indicate the electrical impulses (i.e. 'pacing

spikes') detected by the ECG that coincide with discharge of the pacemaker at a rate of 90 bpm. 25 mm/s; 10 mm/mV. ECG, electrocardiogram.

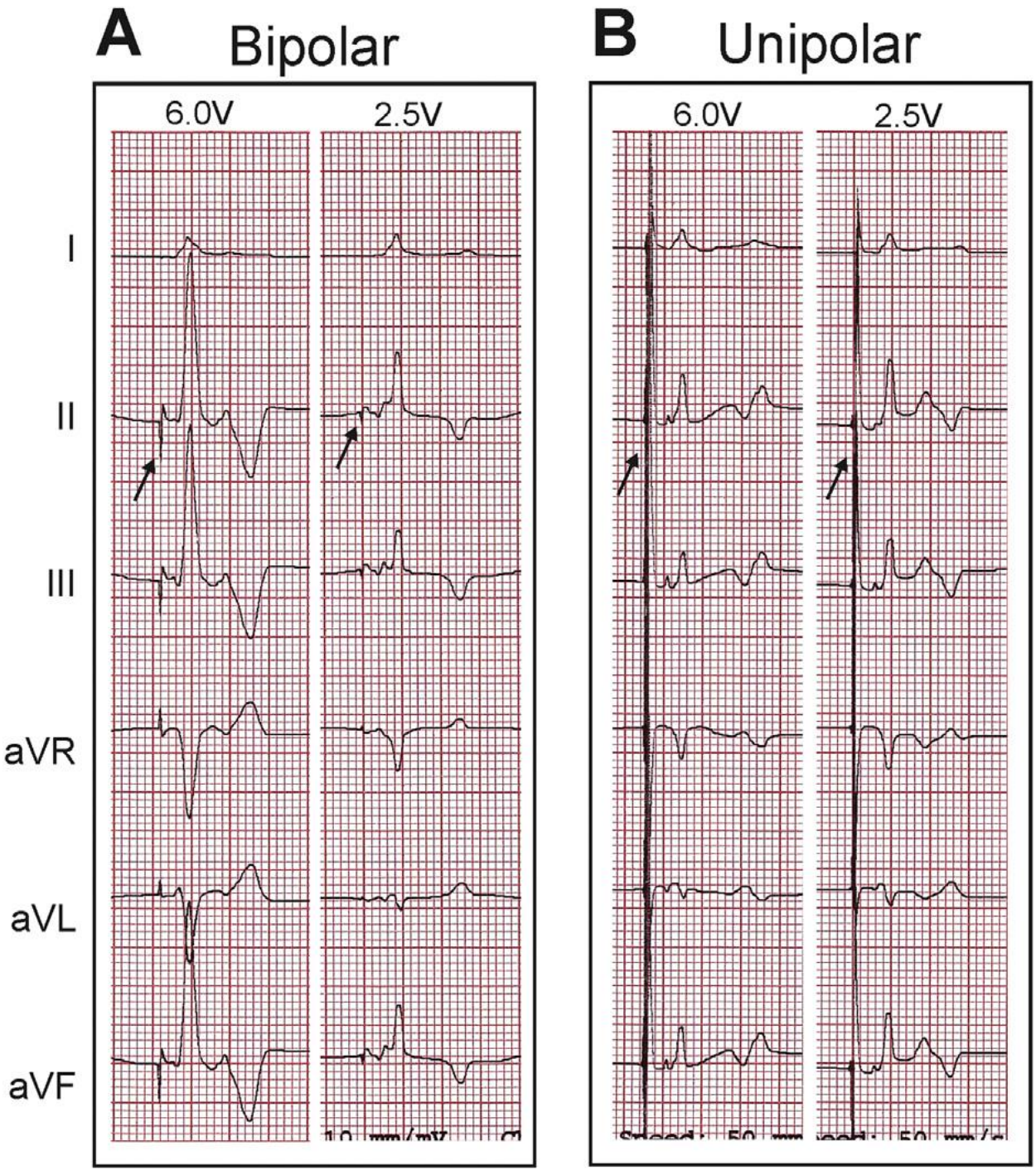

Figure 2. Representative QRS complexes from a 6-lead ECG from dog 2. Fifty millimeters per second; 10 mm/

mV. (A) QRS complexes during bipolar pacing at high (6.0 V) and low (2.5 V) pacing output amplitudes. Note the taller R waves in leads II, III, and aVF and more negative QRS complexes in leads aVR and aVL during pacing at high amplitudes. See text for additional details. The arrows indicate the electrical impulses detected by the ECG (i.e. 'pacing spikes') that coincide with discharge of the pacemaker. (B) QRS complexes during unipolar (6.0 V) and low (2.5 V) pacing output amplitudes. The morphologies of the QRS complexes are not markedly affected by the pacing output amplitude during unipolar pacing, which supports the notion that the change detected during bipolar pacing was due to anodal stimulation at an output of 6.0 V. The arrows indicate relatively large amplitude unipolar electrical pacemaker impulses (i.e. 'pacing spikes') detected by the ECG. See text for additional details. ECG, electrocardiogram.

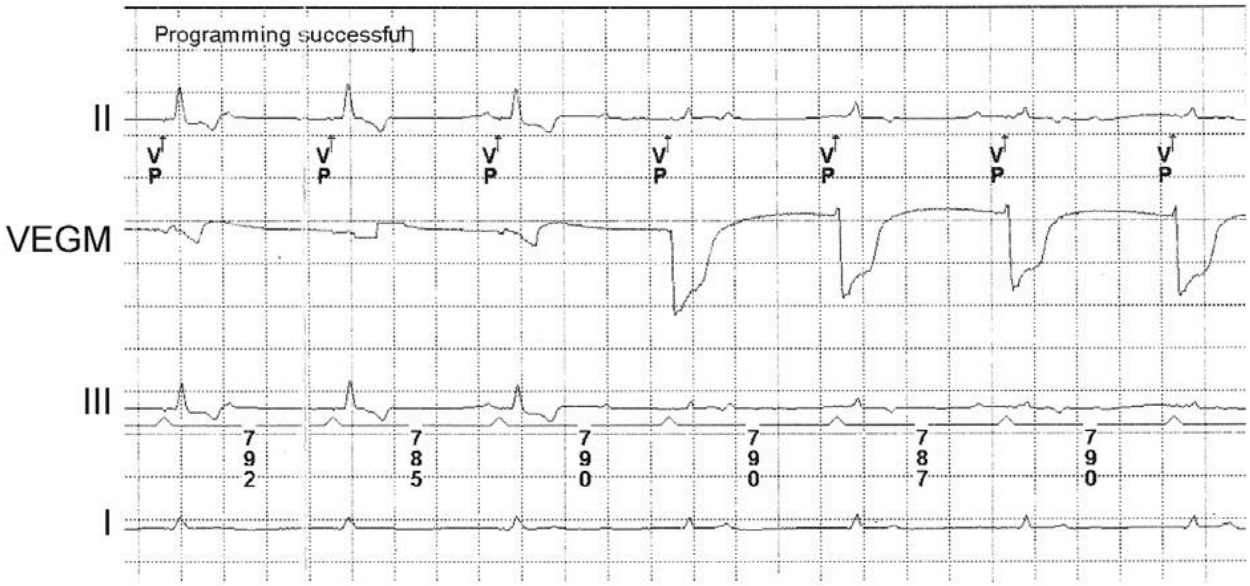

Figure 3. Pacemaker interrogator report from dog 2 displaying ECG leads I, II, and III and the ventricular endocardial electrogram (VEGM) during a programming switch of pacemaker output amplitude from 6.0 V to 2.5 V (arrow marked 'programming successful'). The VEGM represents electrical depolarization as recorded by the pacemaker lead in contact with the ventricular myocardium. Changes in QRS complex morphology recorded by both the ECG and VEGM support an altered sequence of ventricular depolarization vs. artifact as the cause of the morphology change. 'VP' indicates the ventricular pacing discharge of the pacemaker and the cycle length in milliseconds is displayed with the lead III ECG. ECG, electrocardiogram.

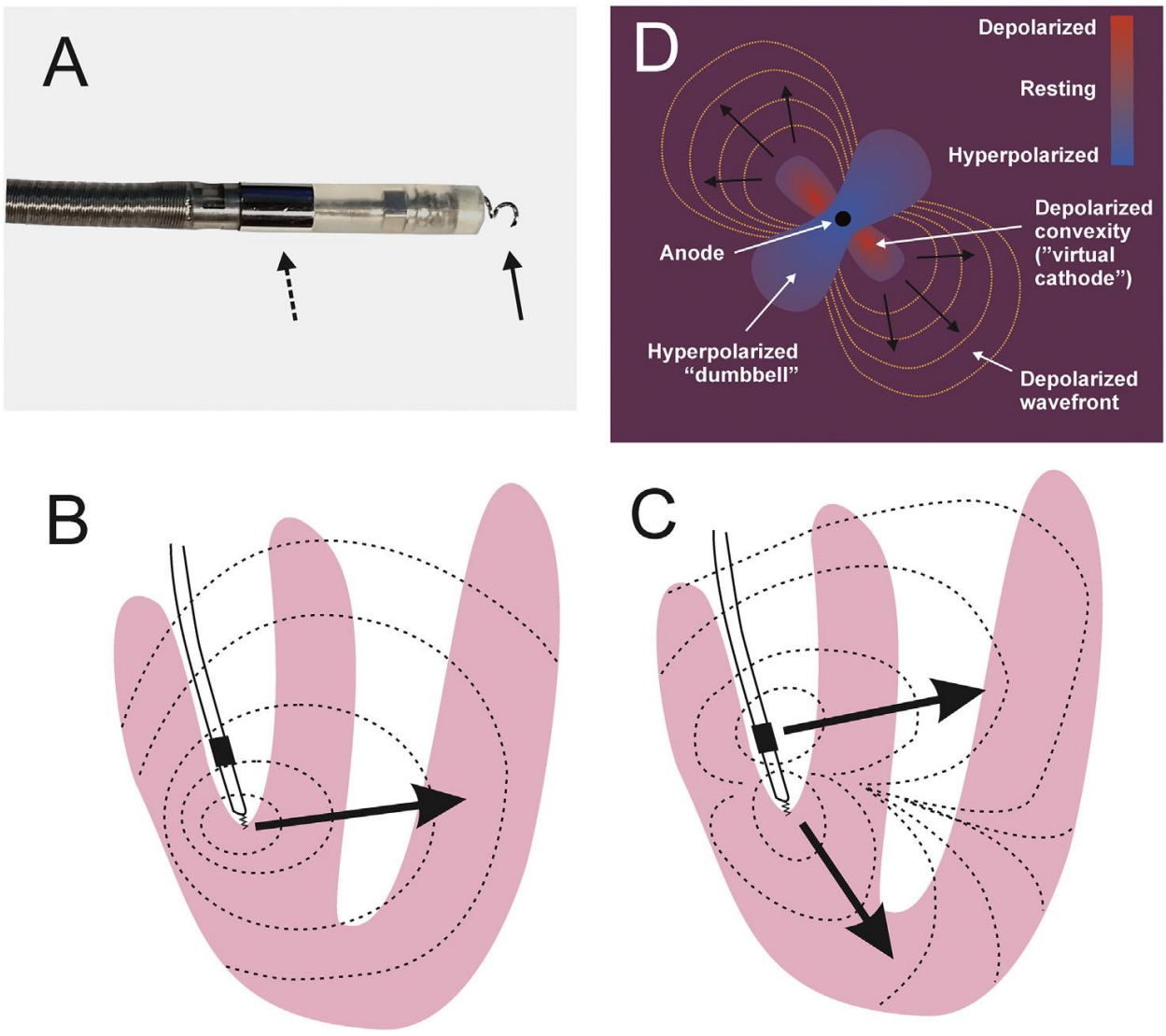

Figure 4. (A) Close up view of the distal end of a bipolar active fixation pacemaker lead. The helical cathode (arrow) has been extended from the body of the lead and is designed to screw into the ventricular myocardium. The anode ring (dotted arrow) is located several millimeters proximal to the end of the lead. In bipolar pacing mode, the helical screw and anodal ring form the electrical circuit with current exiting the cathode and reentering at the anodal ring. In unipolar pacing mode, the anodal ring on the pacemaker lead is inactive and the pacemaker generator is utilized as the anode. (B) Schematic of cathodal stimulation by a right ventricular pacemaker lead and the sequence of right and left ventricular depolarization. The helical cathode

is implanted in the right ventricular apex and serves as the origin of the wave of ventricular depolarization. (C) Schematic of simultaneous cathodal and anodal stimulation by a right ventricular pacemaker lead set to bipolar pacing mode. High pacing output amplitudes causes a wave of depolarization to originate from both the anodal ring and cathodal helix. The resultant sequence of ventricular depolarization is a combination of the two waves and the QRS complex morphology of both the ECG and VEGM would be expected to change as compared to (B). (D) Schematic of the myocardial membrane potentials at the location of the anode. A dumbbell-shaped region of hyperpolarized tissue (blue) surrounds the anode. Within the convexities of this region, two regions of depolarized tissue (red) are created and serve as regions from which an action potential can be triggered. Cardiac depolarization during anodal stimulation is generally thought to originate from these 'virtual cathodes'. Adapted from Wikswo JP et al. [3] ECG, electrocardiogram; VEGM, ventricular endocardial electrogram.

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[b] Dog 1, Sensia SESR01; Dog 2, Adapta ADVDD01, Medtronic, Minneapolis, MN USA
[c] 2090, Medtronic, Minneapolis, MN USA