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CASE REPORT

Successful application of closed loop stimulation pacemakers with remote monitoring in 3 miniature donkeys with syncope

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Abstract
Rate-adaptive single chamber pacemakers with accelerometer, closed loop stimulation (CLS), and remote monitoring functionality (Eluna 8 SR-T, Biotronik, SE & Co, Germany) were implanted in 3 miniature donkeys with third-degree atrioventricular block and syncope. After recovery, different pacemaker programming modes were tested at rest, during stress without physical exercise and during physical exercise. Pacing rates were compared to actual atrial rates and showed that CLS functionality allowed physiological heart rate adaptation. A transmitter installed in the stable provided wireless connection of the pacemaker to the internet. Home monitoring was activated which performed daily wireless transmission of pacemaker functional measurements to an online server allowing diagnosis of pathological arrhythmias and pacemaker malfunction from a distance. Closed loop stimulation and remote monitoring functionality resulted in nearly physiological rate adaptation and allowed remote "from-the-stable" patient follow-up.

KEYWORDS
bradyarrhythmia, collapse, equine cardiology, permanent pacing, third degree atrioventricular block

1 | INTRODUCTION

Third-degree atrioventricular (AV) block is an uncommon bradyarrhythmia in horses and donkeys, which can be associated with inflammatory or degenerative changes in the AV node or can be idiopathic.[1,2] Because of absent conduction from the atria to the ventricles via the AV node, the ventricles depend on their own slow intrinsic rhythm, which may result in syncope.[1] Diagnosis is made by an ECG which shows AV dissociation (ie, P waves no longer associated with QRS complexes). Also, there are more P waves than QRS complexes and often the escape QRS complexes have a widened and bizarre appearance[1] whereas RR intervals may be regular or irregular. This pathology is often irreversible and has been treated successfully by pacemaker implantation in horses and donkeys.[3-7] The pacemaker monitors heart rate and rhythm and induces a cardiac depolarization by delivering an electrical current via an electrode to the myocardium.[1] Single-chamber and dual-chamber pacemakers are available with a variety of programmable pacing modalities.[7] Pacemaker types are described using a letter code where the first and second letters indicate the chamber being paced and sensed, respectively. The third letter indicates the reaction of the pacemaker when an intrinsic beat is sensed. The fourth position reflects the programmability of the device. The letter "R" is noted when the pacemaker incorporates a sensor-based rate modulation and "CLS" indicates closed loop

Abbreviations: AV, atrioventricular; CLS, closed loop stimulation.

stimulation.[3] In veterinary medicine, rate-adaptive pacemakers based on motion sensors have been described.[7-9] In human medicine, recent pacemakers allow heart rate adaptations during emotional and physical stress by the use of CLS whereby local impedance of the myocardium is monitored, and changes with an altered inotropic state of the myocardium.[10-12] In addition, innovative pacemakers allow remote monitoring of pacemaker function and detection of arrhythmias, resulting in better patient follow-up.[13] This case report describes the successful use of CLS and remote monitoring in 3 miniature donkeys with syncope.

2 | CASE HISTORY

2.1 | Clinical features donkey 1

A 149 kg, 7-year-old miniature donkey gelding was presented for revision of a pacemaker that had been implanted 6 years before. As a yearling, the donkey was presented with bradycardia (Figure 1) and syncope caused by third-degree AV block. A modified base-apex ECG (Televet 100, version 6.0, Kruuse) showed occasional periods of AV conduction, but these were associated with abnormal QRS morphology, possibly because of bundle branch block (Figure 2). A left-sided holosystolic (4/6) and holodiastolic (3/6) heart murmur was present and echocardiography showed tricuspid valve dysplasia, mild aortic and mitral valve regurgitation, dilatation of the aortic root 3 cm distal to the valves and a patent ductus arteriosus. A single chamber VVI refurbished pacemaker was implanted. Syncope was no longer observed and regular follow-up showed similar echocardiographic findings. Two years after pacemaker implantation, the donkey was presented for fever and vegetative lesions were found on the tricuspid valve and the ventricular lead. No bacteria could be isolated from peripheral blood culture. The donkey was treated with broad-spectrum antibiotics for 6 weeks. Vegetative lesions decreased in size and no clinical signs were observed over the next 4 years. At the age of 7, because of limited pacemaker battery life, pacemaker revision was required. Upon presentation, the donkey was bright and alert and had a heart rate of 40 beats per minute (bpm), a respiratory rate of 16/min and normal rectal temperature (37.3°C). The ECG disclosed a ventricular-paced rhythm with occasional periods of AV conduction with abnormal QRS morphology and periods of ventricular tachycardia mainly during physical activity or stress. When the pacemaker was switched off, the donkey became syncopal. Echocardiography still showed small vegetative lesions on the tricuspid valve and ventricular lead.

2.2 | Clinical features donkey 2

A 90 kg, 2-year-old miniature donkey stallion was presented with a history of frequent syncope for several months. Upon presentation, the donkey was bright and alert, had a heart rate of 22 bpm, a respiratory rate of 16/min and a normal rectal temperature (37.1°C). Cardiac auscultation identified a left-sided holosystolic (5/6) and holodiastolic (4/6) murmur and right-sided holosystolic (2/6) murmur. The ECG showed third-degree AV block with a ventricular escape rhythm with 2 different QRS morphologies. Occasionally, periods of AV conduction occurred, but those QRS complexes had abnormal morphology and duration. Echocardiography disclosed mild pulmonary valve stenosis, mild aortic and pulmonary valve regurgitation, and dilatation of the aortic root 4 cm distal to the aortic valves.

2.3 | Clinical features donkey 3

A 185 kg, 19-year-old miniature donkey mare was presented with a history of intermittent syncope for 1 year. An ECG performed at the referral clinic showed third-degree AV block. Upon presentation, the donkey was bright and alert with a heart rate of 24 bpm, a respiratory rate of 12/min and normal rectal temperature (37°C). No heart murmur was present. The ECG showed third-degree AV block, an escape rhythm with different morphologies, and episodes of paroxysmal ventricular tachycardia (Figure 3). Echocardiography showed moderate pulmonary valve regurgitation and trace aortic valve regurgitation. The pulmonary artery was dilated.

2.4 | Pacemaker implantation

In donkey 1, the original pacemaker was replaced under general anesthesia by a pacemaker with CLS and home monitoring functionality (Eluna 8 SR-T, Biotronik, SE & Co). The leads implanted 6 years before were left in place. In the remaining 2 donkeys, the same single-chamber pacemaker type with a 60 cm bipolar steroid-eluting screw-in lead (Solia S 60, Biotronik, SE & Co) was implanted in the right ventricular apex under general anesthesia, similar to the previously described methodology in standing horses.[6] In brief, before implantation in the standing donkey, a temporary bipolar pacing catheter (Biosense Webster EZ steer bidirectional CS catheter, Biosense Webster, Johnson and Johnson, Irvine, California) was inserted into the right jugular vein and positioned in the right ventricular apex under ultrasound guidance to obtain temporary pacing (Carelink 9790, Medtronic or EDP 20/B, Biotronik, SE & Co) during the implantation procedure (Figure 4). Subsequently, the donkey was placed under general anesthesia in left lateral recumbency. After surgical preparation, the right cephalic vein was isolated, and the endocardial bipolar screw-in lead was inserted. Guided by echocardiography (GE Vivid 7 Dimension or Vivid IQ, GE Healthcare, Diegem, Belgium, phased array transducer 3.5-8 MHz) and the intracardiac electrogram (Televet 100 Special, version 6.0, Kruuse), the ventricular lead was positioned in the right ventricular apex and the screw was extended into the endomyocardium (Figure 4). The ventricular lead was connected to the pacemaker, which was positioned SC between the lateral pectoral groove and the manubrium sterni. The SC tissue and skin were closed in a routine manner. The pacemaker was programmed in VVI mode (ventricle-paced, ventricle-sensed, inhibited response to sensing) at a rate of 40 bpm and the temporary pacing catheter was removed.

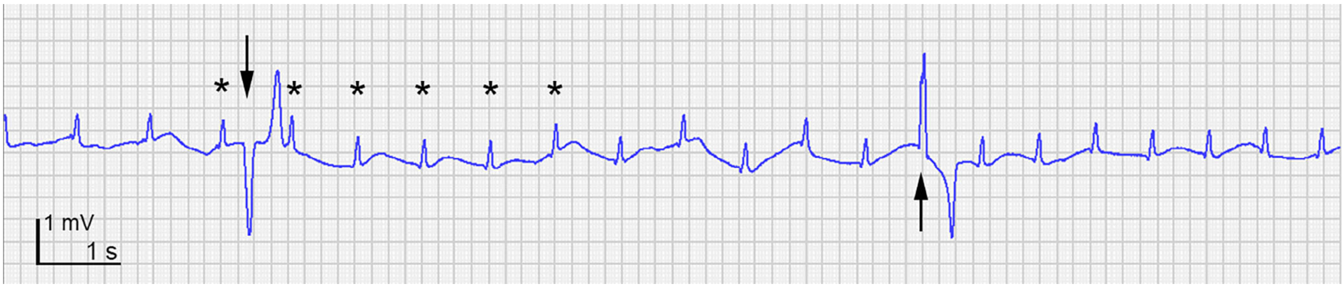

FIGURE 1 Modified base-apex ECG from donkey 1 before pacemaker implantation shows atrioventricular dissociation, with P waves (*) occurring at a rate of 79/min, while ventricular escape rhythm is very slow. The time between both QRS complexes of different morphology (arrows) is 8 seconds

FIGURE 2 (A) A modified base-apex ECG of donkey 1 shows association between P waves and QRS complexes, indicating temporary atrioventricular conduction. The QRS complexes are broadened and have an abnormal morphology, which might be caused by bundle branch block. For comparison, (B) the ECG of a healthy donkey, taken with an identical electrode position, is shown. These normal QRS complexes have a shorter duration and different morphology

During postoperative hospitalization, a bandage was placed over the pacemaker implantation site for 18 days. Nonsteroidal anti-inflammatory drugs and broad-spectrum antibiotics were administered over 3 to 5 days. No complications were observed except slight SC swelling for the first few days. Pacemaker characteristics, such as pulse amplitude and duration to reach pacing threshold, sensing amplitude, and lead impedance,[3,14,15] were checked repeatedly over the next 2 to 3 weeks and adjusted by transcutaneous programming to ensure good capture. Echocardiography was performed to confirm stable lead position.

2.5 | Pacemaker programming mode

After the recovery period, in each donkey, 3 different pacemaker programming modes were compared at rest, during stress without physical activity and during physical activity. A modified base-apex ECG was recorded during the test. Over 20 consecutive beats, atrial rate (PP intervals) and paced ventricular rate (RR intervals) were determined. Programming modes included the nonrate adaptive VVI mode (VVI), an accelerometer-based rate-adaptive mode (VVIR) and a CLS-based rate-adaptive mode (VVI-CLS). Minimal ventricular rate was

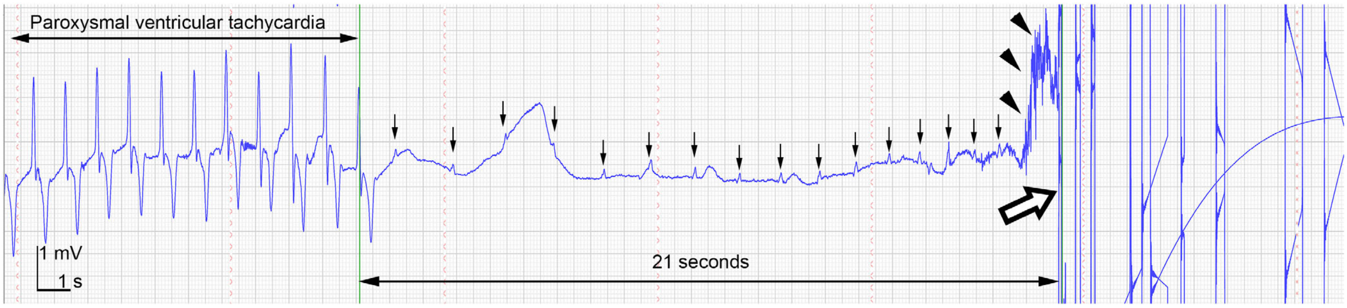

FIGURE 3 A paroxysm of ventricular tachycardia in donkey 3 is followed by complete atrioventricular block during which only P waves (arrows) can be identified. Nineteen seconds after the last QRS complex, the donkey starts trembling (arrow heads), visible as small spikes. Twenty-one seconds after the last QRS, the donkey collapses (open arrow)

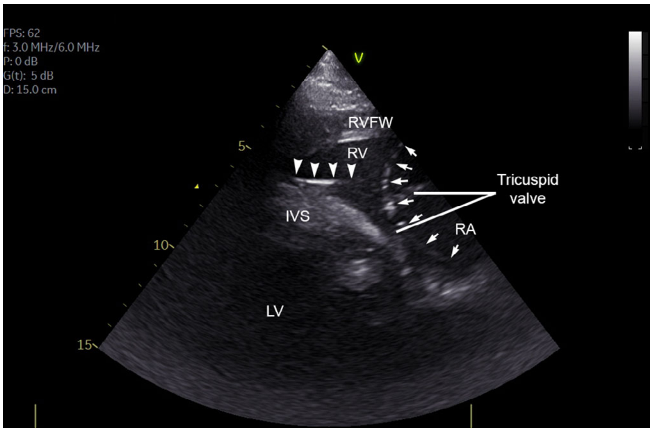

FIGURE 4 Echocardiographic image from donkey 3, taken during the implantation procedure. A steerable decapolar pacing catheter (white arrows) is inserted through the right atrium (RA) into the right ventricle (RV). The tip of this catheter is positioned against the high right ventricular free wall (RVFW) to perform temporary ventricular pacing during the implantation procedure. The ventricular lead (white arrowheads) of the pacemaker has been inserted and fixated into the right ventricular apex. Using a steerable pacing lead facilitates the differentiation between both wires during the implantation procedure. IVS, interventricular septum; LV, left ventricle

programmed at 40 bpm. In the VVIR mode, rate adaptation was achieved by detection of body motion by the built-in activity sensor. The sensor gain and threshold were arbitrarily set at medium with an upper rate of 100 bpm, which restricts the highest rate that the pacemaker will produce. Rate fading was set on, rate increase at 2 bpm per cycle and rate decrease at 1 bpm per cycle. In the VVI-CLS mode, the sensor gain and sensor threshold were arbitrarily set at medium with an upper rate of 120 bpm and a CLS resting rate control at +10 bpm relative to the basic pacing rate.

First, data were recorded while the donkey was standing still in a quiet environment (rest). Subsequently, a sudden noise was introduced while someone suddenly entered the stable so as to evoke stress. Data was judged valid when the donkey remained in the same position, without physical movement. Finally, heart rate was evaluated at walk or trot (physical activity). Data are presented in Table S1. Compared to VVI and VVIR, the mean ventricular rate in VVI-CLS was higher at rest, during stress, and during physical activity. The atrial rate was higher than the ventricular rate in all settings. Because donkey 1 presented with AV conduction in VVI mode during stress and physical activity, a mean paced ventricular rate could not be obtained.

2.6 | Remote monitoring

Before discharge, the active capture control function of the pacemaker was activated. With this functionality, the pacemaker performs a threshold test once a day and automatically adapts the pulse strength if needed. This feature saves battery life because excessive pacemaker output is avoided. Also, the remote monitoring functionality (Biotronik Home Monitoring, Biotronik, SE & Co) was activated. The home monitoring receiver ("CardioMessenger Smart" Biotronik, SE & Co), a small box approximately the size of a smartphone, was installed in the stable where the donkey stayed at night either alone or with companions. On a daily basis, at a fixed time point, the pacemaker transferred functional variables wirelessly to the receiver, which exchanged data through the mobile network to an online server. These data included pacemaker settings, pacemaker characteristics such as battery status, lead impedance, R wave sensing amplitude, pacing threshold, and pacing percentage, and patient characteristics such as paced heart rate, thoracic impedance and patient activity. At any time, the clinician can login to the server to verify the data. The server also automatically analyzes the data and in case of suboptimal pacemaker function or ventricular tachycardia, automatically sends warning messages to the clinician. All donkeys were discharged with the pacemaker in VVI-CLS mode.

Three years after implantation, donkey 2 was presented because of fever (40°C) and chronic weight loss of 3 weeks' duration. The donkey had lost approximately 20% of its body weight and the white blood cell count was markedly increased. The pacemaker was still functioning well, but echocardiography showed large echogenic vegetations on the tricuspid valve. At the owner's request, the donkey was returned home to start broad-spectrum antibiotic treatment, but died of septicemia the same day. At the time of writing, donkeys 1 and 3 remained free of clinical signs and have been implanted for 8 years and 1 year, respectively.

3 | DISCUSSION

This case report describes the first successful clinical application of a pacemaker with VVI-CLS mode and remote monitoring in veterinary medicine. This type of pacemaker allows automatic heart rate adaptation and remote monitoring of pacemaker function by data exchange between the pacemaker and an online server.

In this report, all of the donkeys were miniature donkeys. The cause of their third-degree AV block was not known, but a genetic predisposition has been suggested.[16,17] Intermittent AV conduction with abnormal QRS morphology, possibly caused by bundle branch block, and paroxysmal ventricular tachycardia also were identified. Two donkeys were diagnosed with aortic root aneurysm several centimeters distal to the aortic valve, which remained stable during the follow-up period (3 and 6 years). One of these 2 donkeys also had a patent ductus arteriosus and tricuspid dysplasia. Whether or not these conditions were related to the AV block remains unknown.

Two of the 3 donkeys developed pacemaker lead endocarditis. Endocarditis has been described previously as a complication of pacemaker implantation in horses.[18] In human patients and dogs, the risk for endocarditis is 0% to 13%[19] and 0% to 19%,[20] respectively. Several studies in human medicine have shown a relationship between the use of temporary pacing wires at the time of implantation and pacemaker-related infections.[20,21] Also, the use of a refurbished device could have played a role. However, in those cases, infection usually occurs within the first year after implantation, whereas late infections usually are attributed to hematogenous colonization. In the donkeys, endocarditis occurred 2 and 3 years after implantation.

In the nonrate-adaptive VVI mode, the pacemaker maintains a minimal ventricular rate without rate adaptation during stress or exercise.[1] In VVIR, rate modulation, based on a built-in activity sensor, provides chronotropic support in case of higher metabolic need.[22-24] In human medicine, limitations of this mode include a need for sufficient thorax motion to drive the heart rate.[23] Body motion is not necessarily correlated with metabolic needs and vice versa. Sometimes an increased metabolic demand is caused by excitement, anxiety, or fear and cannot be sensed by an activity-driven pacemaker.[8] In VVI-CLS mode, the pacemaker also measures the intracardiac impedance of the ventricular myocardium throughout each ventricular contraction. Reference curves are created by using the average of the last 256 curves of the paced and sensed events. A change in myocardial contractile function results in a change of myocardial thickness and impedance.[10] The larger the difference between the measured impedance and the reference curve, the higher the pacing rate. Early detection of these changes leads to immediate and automatic adaptation of the pacing rate and thus improved cardiac output during emotional stress and physical activity.[11,12] We showed that this feature functioned properly in donkeys as well. Little is known about resting heart rates and heart rate responses during exercise in donkeys. We attempted to use the PP interval to approximate the physiological target rate. However, PP rate may be higher than expected because of stress, as observed in donkey 3, or because of hypotension when ventricular rate is not sufficiently high.

The pacemaker allowed sophisticated adjustment of the rate adaptation in VVIR and VVI-CLS modes. Settings such as sensor threshold and sensor gain allow patient-specific fine tuning of the rate adaptation. We selected the medium settings and did not further attempt to improve rate response settings because exercise testing in the donkeys proved to be very challenging. The test was done by walking and trotting for which the donkey needed substantial encouragement which in turn was associated with a stress response. Because the exercise test was not reproducible and the donkeys were not intended to be ridden or harnessed, the importance of rate adaptation probably was limited. Therefore, our results for the rate response in VVIR and VVI-CLS should be interpreted with caution. However, physical effort and even stress were correctly identified and led to an increase in heart rate. Therefore, it seems likely that this pacemaker type (and especially the CLS functionality) can be used in other species as well.

In human medicine, remote monitoring is extremely useful for early detection of device malfunction and for monitoring cardiac arrhythmias, patient activity, and heart rate.[13] The remote monitoring system used in our study is based on continuous monitoring by the pacemaker with daily transmission of diagnostic data. In addition, automatic alerts to the clinician in case of device malfunction allow rapid intervention. This feature allowed diagnosis of brief episodes of ventricular tachycardia in donkey 1. The receiver should be installed near the patient which proved to be feasible in a stall-side situation. The automatic capture control regularly adapts the pacemaker stimulus output to the results of an automatic threshold test. In combination with the remote monitoring, the clinician can follow pacemaker functionality and automatic adaptations from a distance, which facilitates patient follow-up.

In conclusion, CLS and remote monitoring are functionalities that can be applied in veterinary medicine and likely will benefit management of bradycardic patients with clinical signs.

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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

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

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

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SUPPORTING INFORMATION

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