Detection of paroxysmal atrial fibrillation preceding persistent atrial fibrillation in a horse using an implantable loop recorder with remote monitoring

Short title: Remote arrhythmia monitoring in a horse

Ingrid Vernemmen[a], DVM, Glenn Van Steenkiste[a], DVM, PhD, Annelies Decloedt[a], DVM, PhD, Hans Meert[b], Ulla Walser[b], Gunther van Loon[a], DVM, PhD.

[a] Equine Cardioteam Ghent, Department of Internal Medicine, Reproduction and Population Medicine, Ghent University, Salisburylaan 133, 9820 Merelbeke, Belgium.

[b] Biotronik Belgium, Medialaan 36, 1800 Vilvoorde, Belgium.

Corresponding author: Ingrid Vernemmen, Ingrid.Vernemmen@ugent.be

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Abstract

Implantable loop recorders (ILR) are increasingly used in equine cardiology to detect arrhythmias in the context of collapse, poor performance or monitoring for recurrence of atrial fibrillation (AF). However to date, the ILR has never been reported to be used with a remote monitoring functionality in horses, therefore the arrhythmia is only discovered when a clinician interrogates the ILR using dedicated equipment, which might delay diagnosis and intervention. This case report describes the use of an ILR with remote monitoring functionality in a horse with recurrent AF. The remote monitoring consisted of a transmission device located in the stable allowing daily transmission of arrhythmia recordings and functioning messages to an online server, available for the clinician to evaluate without specialised equipment. The ILR detected an episode of paroxysmal AF approximately 3 months after implantation. Seven months after implantation initiation of persistent AF was seen on an episode misclassified by the ILR as bradycardia, and the horse was retired. This report shows the feasibility and benefits of remote monitoring for ILRs in horses, but also the shortcomings of current algorithms to interpret the equine electrocardiogram.

Keywords

Insertable cardiac monitor, event recorder, home monitoring, arrhythmia, telemetry

Introduction

Atrial fibrillation (AF) is the most important arrhythmia affecting performance in equine athletes [1]. It can be classified in paroxysmal AF, which usually converts spontaneously within 24-48 h, and persistent AF, which requires electrical or pharmacological cardioversion. Atrial fibrillation not responding to treatment is called permanent AF [2]. Clinical signs include poor performance, exercise-induced pulmonary haemorrhage, prolonged recovery and respiratory distress after exercise and occasionally weakness or collapse during exercise [3, 4, 5]. However, clinical signs are often subtle or even absent, especially at rest due to the high vagal tone in horses. For this reason, early diagnosis can be challenging, particularly in cases with paroxysmal AF [2]. In this context, the use of implantable loop recorders (ILRs) can be of interest. An ILR is a small device which is implanted subcutaneously and continuously monitors the individual's heart rate and rhythm. Depending on its settings, it will store data and short electrocardiogram (ECG) tracings of arrhythmic events, thus facilitating earlier diagnosis of arrhythmias such as AF. The use of ILRs in horses has been reported previously for investigation of the underlying cause of collapse [3, 6] and intermittent poor performance [7] and for monitoring AF recurrence [8]. However in these cases, a clinician needed to interrogate the device with dedicated equipment in order to extract the data recorded by the device to check whether an arrhythmia had been recorded or not. This can delay diagnosis of arrhythmias that are not always associated with clinical signs, such as paroxysmal or persistent AF. In this report, we present the use of an ILR with remote monitoring functionality for improved diagnosis of AF in a horse.

Case history

A 6-year-old trotter gelding, used for harness racing, was admitted to the Equine Cardioteam Ghent, Faculty of Veterinary Medicine, Ghent University for AF recurrence with a suspected duration of 2 months. The horse had already been treated twice by transvenous electrical cardioversion 10 months and 7 months before. On echocardiographic examination no abnormalities were seen except for a low left ventricular fractional shortening (23 %), mild mitral and mild tricuspid regurgitation. The right atrial intracardiac fibrillation cycle length at the intervenous tubercle was 140 ms, which was lower than the cycle length during the previous AF episodes (first episode: 180 ms, second episode: 156 ms). Despite the high risk for recurrence, another electrical cardioversion was performed, as described elsewhere [9] and conversion was achieved after the third shock at 250 Joules (150 J and 200 J unsuccessful). Anti-arrhythmic treatment with phenytoin (10 mg/kg PO q 12 h for 4 weeks) was started directly after recovery.

On day 1 and day 5 post-cardioversion echocardiographic follow-up examinations were performed. Based upon left atrial active fractional area change [10], atrial contractile function was recovering slowly (day 5: 6 % (ref. 11.6 - 23.2 %)). On day 5 post-cardioversion, a 12-hour electrocardiogram recording showed 18 atrial premature complexes. Since these results further increased the risk for AF recurrence [11], it was decided to implant an ILR[c], BioMonitor 2-AF, on day 6 post-cardioversion in order to monitor cardiac rhythm and potential AF recurrence.

Using a smartphone-based ECG recording device[d], the location and orientation for the ILR were determined by looking for large P waves, large QRS complexes and small T waves, whilst ascertaining that it would not interfere with the girth. The fifth intercostal space at the level of the left deltoid tuberosity with an orientation of approximately 60°

in a craniodorsal-caudoventral direction was chosen. In the standing sedated horse, after surgical preparation and local anaesthesia of the implantation site, a 2 cm wide skin incision was made. Using the dedicated tool, the subcutaneous tissue was bluntly dissected after which the ILR was released in the determined position using the insertion tool. The incision site was stapled using four staples and covered with a bandage. On the day of implantation and the 3 following days, the horse was treated with 1.1 mg/kg PO flunixin meglumin and 20,000 IE/kg IM procaine benzylpenicillin. The ILR was programmed as follows: R wave sensing threshold 500 µV; bradycardia detection on (detection of a heart rate of less than 30/min over more than 20 seconds); detection of AF on. Bradycardia detection was activated to retrieve sufficient ECG data to monitor the heart rhythm. The AF detection was based on an RR interval variability limit of 12.5 % (default). The ILR would detect an episode of AF if five out of eight consecutive cycles exceeded the RR interval variability limit, and the AF episode would be considered terminated if maximally three out of 16 consecutive cycles exceeded the RR interval variability limit. If over a period of three minutes no termination of AF would be detected, the episode would be stored as 'AF'. Locally, the ILR can store up to 55 events with corresponding ECGs (length: 40-60 s per episode), and when overwriting is needed, the newest, oldest and longest episode of each arrhythmia are prioritized for local storage. These episodes can be evaluated by interrogation using the dedicated programmer. The remote monitoring functionality[e] was activated as well. This technique allows daily data transfer from the ILR to an online server via the 4G network, similar as previously described for pacemakers [12]. It requires the positioning of a small device, the remote monitoring receiver/transmitter[f], in or near the box of the horse (within a radius of approximately 4 meters). After arrhythmia detection and data transfer, this remote monitoring allows immediate messaging of the responsible clinician via email and early diagnosis within 24 hours of the event. Apart from the messages summarizing the arrhythmic events, also the corresponding ECG traces from the most recent recordings of each type of arrhythmia are transferred with a maximum of six events per 24 hours. In addition, monitoring ECGs are transmitted at pre-defined intervals (in this case every 30 days) which allows for checking device function in case no arrhythmias occur. The clinician is also notified if during a predetermined number of days no messages were received by the server, which was set to 21 days for this horse. The horse was discharged on the 4th day post-implantation.

An overview of the online transmission of ECG recordings by the ILR is given in Table 1. In the following 4 months, a total of 358 recordings (classified as bradycardia or AF) were made by the ILR and transmitted to the online server. The majority of these recordings were false positive detections of mainly bradycardia, however, one recording approximately 3 months after implantation showed an episode of AF of at least 26 minutes of duration (Fig. 1). The onset of the AF episode was not visible on the recording. In addition, on interrogation of the device another episode of AF was visible on the day after the detected episode (not present on the server probably due to no connection with the transmission device), with a presumed length of 8 hours. It was unclear if these consisted of two separate episodes or one long episode. The day after this episode, sinus rhythm was visible on the transmitted ECGs. One month after this paroxysmal AF episode, in an attempt to reduce potential AF triggers from the myocardial sleeves of the caudal vena cava, radiofrequency energy catheter ablation following three-dimensional electro-anatomical mapping was performed to try and isolate these myocardial sleeves, as previously described [13]. However, a non-contact force mapping system was used and point-by-point radiofrequency ablation failed to isolate the myocardial sleeves as pacing capture was still present. In the following 3 months, 449 recordings (277 'bradycardia', 172 'AF') were stored by the ILR, of which all AF events and 44 % of bradycardia events were misclassified. Seven months after implantation, initiation of AF was detected on a recording misclassified as bradycardia due to QRS undersensing (Fig. 2). All subsequent recordings (N = 105) showed presence of persistent AF.

From the day of implantation until the day of confirmation of persistent AF (229 days), the ILR transmitted a median of six recordings per day (range 0-6 recordings). There were zero recordings on 91 days (40 %), which included a prolonged period of 13 and of 11 days, because the horse temporarily did not enter the box with the transmission device. QRS amplitudes increased over the follow-up period from a mean value per week of 390 µV in the first week to 790 µV in the last week of transmitted recordings, however on ECG recordings these values showed to be very variable. No further treatment was proposed and the horse was retired, the transmission of arrhythmia alerts was terminated 20 days after the start of AF.

Discussion

This case report presents the use of an ILR with remote monitoring functionality to diagnose paroxysmal AF and progression to persistent AF in a horse after electrical cardioversion. Although originally designed as a bedside tool for human medicine, data transfer was shown to be feasible in a standard stable environment. It requires a receiver/transmitter, functioning on battery or mains power, in the stable of the horse. Daily data transfer occurs at a predetermined time, when the horse should be at a maximal distance of about 4 meters from the receiver/transmitter. Remote monitoring reduces the need for frequent follow-up exams with dedicated equipment in hospital or by a clinician, allows for more rapid intervention in case of abnormalities, and reduces the risk for missing paroxysmal events as more data can be stored online. Apart from the initial purchase cost of the remote monitoring system, once the device has been implanted and programmed, no specialised expensive equipment is needed for regular follow-up, as all data can be accessed via internet. Also the intervals between monitoring ECGs can be adapted remotely. In human medicine, remote monitoring has additionally been shown to be beneficial to the patient's perceived relationship to the healthcare provider, mental status and compliance to follow-up examinations [14], which might be translatable to horse owners. Since implantation was performed on the standing sedated horse, empirical antibiotic treatment was given on the day of implantation and three days post-implantation. In previous reports of ILR implantations in horses, no prophylactic antibiotic treatment was given and no infections were observed [7, 8, 15].

The ILR was implanted in a similar way as reported by Buhl et al. [7, 15], however using another device with a different AF detection algorithm. In comparison to these studies, the number of false positive detections of AF was considerably higher in our case. False positive alerts are also common in humans, with especially high false discovery rates of up to 74.2 % and 76.8% for AF and asystole alerts, respectively [16]. The asystole alerts have mainly been attributed to R wave undersensing, which is similar to our case, however false positive AF alerts in human patients are mainly caused by frequent ectopy with only a minor proportion caused by over- or undersensing. This is in contrast to our horse, in which T wave detection due to a low QRS/T wave amplitude ratio (Fig. 3) was the main cause of the false positive alerts, thus bypassing the adaptive thresholds in the sensing algorithm designed to reduce T wave sensing [17]. Although P wave size was also taken into account when determining the implantation site, the number of false positives due to P wave oversensing turned out to be low. It has been shown that QRS amplitude during implantation is not necessarily predictive for QRS sensing during follow-up [18]. Both in humans [18] and horses [15] QRS amplitudes captured by ILRs are known to be variable. This has been related to posture in humans, emphasizing the importance of selecting an implantation site with minimal movement of the ILR [19]. Not all sensing settings to reduce T wave sensing in favour of QRS sensing have been explored in our horse, and could have reduced the number of false positive alerts. By adjusting the sensing threshold, sensing decay and the high pass filter, the settings might have been better adapted to the variable QRS amplitude and high T waves. In addition, other available devices and algorithms might be better adapted, and the advent of artificial intelligence might reduce the workload for veterinarians in the future [20]. Because of the numerous alerts (maximum of 6/day), the current combination of implantation location, ILR type and ILR settings resulted in a time-consuming follow-up.

The high number of false positives might have resulted in missing true positive events, as only the most recent events per type of arrhythmia are stored, and theoretically a true AF event early in the day might not have been transmitted to the server due to multiple false positive AF detections later that day. This can partly be mitigated by interrogating the ILR on a regular basis, as events not transmitted to the server might still be stored on the device, however this would undermine the advantage of remote monitoring. Nevertheless, local storage on the ILR device proved to be useful as an episode of AF not transmitted to the server (probably due to no connection to the transmission device that day) could be detected in this manner.

The high load of arrhythmia alerts in our case was for a large part caused by bradycardia detections for which the false discovery rate improved over time, although no settings were changed during the follow-up period and no learning process is involved in the algorithm of the ILR. It might have been related to the increased amplitudes leading to less QRS undersensing. Similarly, the false discovery rate for AF detection improved as well, however, this was due to the fact that the prevalence of actual AF increased in this period. The bradycardia detection was activated to receive sufficient data to monitor the heart rhythm, especially for short paroxysms of AF which would last less than three minutes. This resulted in the maximum of arrhythmia alerts per day during the majority of the follow-up and therefore theoretically only short AF episodes in between the bradycardia alerts or missed by the AF detection algorithm could have been missed. However, due to the transmission of only the most recent events to the server and the frequent occurrence of false bradycardia detections, daily distribution of ECGs was not as high as intended and unidentified AF events happening earlier that day would still be missed. Nonetheless, the onset of the persistent AF was accidentally discovered on a misclassified bradycardia episode.

In human medicine, AF is known to be progressive due to atrial remodelling, starting with paroxysmal AF and eventually evolving towards persistent and even permanent AF [21, 22]. In horses, paroxysmal AF is mainly diagnosed in racehorses with poor performance during the postrace period [7, 23, 24, 25, 26], although it was recently detected using an ILR in two horses during a resting period [7, 8]. These horses were treated for persistent AF prior to ILR implantation, similarly to the horse in our case report. These three cases show that paroxysmal AF, which is difficult to diagnose [25, 27], is probably more important in the pathophysiology of AF in horses than currently thought and can lead to AF progression by inducing electrical, contractile and structural remodelling, similar to acute AF episodes [28, 29, 30]. Recurrence of AF after paroxysmal AF has recently been reported in a retrospective study of racing records in Hong Kong [23], which likely demonstrates its role in the atrial remodelling promoting

AF. Increased use of ILRs and advances in computer-based ECG analysis should provide more insight in the prevalence of paroxysmal AF and its role in AF pathophysiology [7, 27].

Early rhythm control using anti-arrhythmic drugs or by pulmonary vein isolation is increasingly advocated in human medicine to counter progression to persistent AF [22, 31, 32]. As long-term anti-arrhythmic medical therapy is unfeasible in a competition setting in horses, ablation strategies seem to be an attractive treatment option. However, further research is needed to unravel the hotspots for triggered activity and re-entry circuit maintenance in horses. Recent findings seem to suggest a potential role for the myocardial sleeves of the caudal vena cava[g] [13] and/or the pulmonary veins [33, 34] as predilection sites. Isolation of the myocardial sleeve of the caudal vena cava was probably not successful in this case as the ablation was performed without contact force monitoring or local impedance measurement, both necessary to ensure adequate tissue contact and lesion formation.

This report shows that remote monitoring of ILRs is feasible in horses, allowing early recognition of arrhythmias and thus creating perspective for rapid intervention. Further refinement of device settings, detection algorithms or combination with artificial intelligence is needed to reduce the false discovery rate for equine arrhythmias.

Conflict of interest

The authors have no conflict of interest to disclose.

Footnotes

[c] BioMonitor 2-AF, Biotronik SE & Co. KG, Berlin, Germany.

[d] KardiaMobile AC-009 with AliveECG vet application, AliveCor Inc., Mountain View, California, USA.

[e] Biotronik Home Monitoring, Biotronik SE & Co. KG, Berlin, Germany.

[f] CardioMessenger Smart, Biotronik SE & Co. KG, Berlin, Germany.

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Tables

Table 1. Overview of recordings stored by the implantable loop recorder and transmitted to the online server. AF: atrial fibrillation; ILR: implantable loop recorder; N: number of recorded episodes.

Time	Episodes	N	True positive	False positive	Reason for false positive (N, % of false positive alerts)	Positive predictive value†	False discovery rate‡
Implantation ILR – Ablation (4 months)	*all*	358	19	339	*(see below)*	5 %	95 %
	AF episodes	88	1	87	T wave sensing (N=73, 84%) Artefacts (N=6, 7 %) P wave sensing (N=3, 3 %) Undersensing (N=3, 3 %) Sinus arrhythmia (N=1, 1 %) No clear reason (N=1, 1 %)	1 %	99 %
	Bradycardia episodes	270	18	252	Undersensing (N= 248, 98 %) Artefacts (N=4, 2 %)	7 %	93 %
Ablation – end of transmission (4 months)	*all*	554	261	293	*(see below)*	47 %	53 %
	AF episodes	277	105	172	T wave sensing (N=155, 90 %) Artefacts (N=9, 5 %) P wave sensing(N=6, 3 %) Undersensing (N=1, 1 %) No clear reason (N=1, 1 %)	38 %	62 %
	Bradycardia episodes	277	156	121	Undersensing (N=120, 99 %) Artefacts (N=1, 1 %)	56 %	44 %

† = (True Positive/N) * 100 ; ‡ = (False positive/N) * 100

Figure legends

Figure 1. Episode of paroxysmal atrial fibrillation detected by the implantable loop recorder 3 months after implantation of the implantable loop recorder. Intervals between ventricular sensed signals are displayed in ms. AF: atrial fibrillation; SECG: subcutaneous electrocardiogram; Vs: ventricular sensed signals.

Figure 2. Initiation of atrial fibrillation after a misclassified episode of bradycardia. Note how the change in amplitude and direction of the QRS complex results in undersensing (°), but also oversensing of T waves (*). Intervals between ventricular sensed signals are displayed in ms. AF: atrial fibrillation; Brady: bradycardia; SECG: subcutaneous electrocardiogram; Vs: ventricular sensed signals.

Figure 3. Example of T wave detection (*) due to changes in QRS amplitude and direction, and increase in T wave amplitude, resulting in a false positive detection of atrial fibrillation. Intervals between ventricular sensed signals are displayed in ms. AF: atrial fibrillation; SECG: subcutaneous electrocardiogram; Vs: ventricular sensed signals.