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Electrocardiographic characteristics of trained and untrained standardbred racehorses

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Abstract

Background: Long-term exercise induces cardiac remodeling that potentially influences the electrical properties of the heart.

Hypothesis/objectives: We assessed whether training alters cardiac conduction in Standardbred racehorses.

Animals: Two hundred one trained and 52 untrained Standardbred horses.

Methods: Cross-sectional study. Resting ECG recordings were analyzed to assess heart rate (HR) along with standard ECG parameters and for identification of atrial and ventricular arrhythmias. An electrophysiological study was performed in 13 horses assessing the effect of training on sinoatrial (SA) and atrioventricular (AV) nodal function by sinus node recovery time (SNRT) and His signal recordings. Age and sex adjustments were implemented in multiple and logistic regression models for comparison.

Results: Resting HR in beats per minute (bpm) was lower in trained vs untrained horses (mean, 30.8 ± 2.6 bpm vs 32.9 ± 4.2 bpm; $P = .001$). Trained horses more often displayed second-degree atrioventricular block (2AVB; odds ratio, 2.59; $P = .04$). No difference in SNRT was found between groups (n = 13). Mean P-A, A-H, and H-V intervals were 71 ± 20, 209 ± 41, and 134 ± 41 ms, respectively (n = 7). We did not detect a training effect on AV-nodal conduction intervals. His signals were present in 1 horse during 2AVB with varying H-V interval preceding a blocked beat.

Conclusions and Clinical Importance: We identified decreased HR and increased frequency of 2AVB in trained horses. In 5 of 7 horses, His signal recordings had variable H-V intervals within each individual horse, providing novel insight into AV conduction in horses.

KEYWORDS
athlete's heart, atrioventricular conduction, cardiac arrhythmia, equine, His signal, sinus node recovery time, specialized conduction system

Abbreviations: 2AVB, second-degree atrioventricular block; APC, atrial premature complex; AV, atrioventricular; EGM, electrogram; HR, heart rate; LV, left ventricle; OR, odds ratio; PCL, pacing cycle length; SA, sinoatrial; SAN, sinoatrial node; SNRT, sinus node recovery time; SV, stroke volume; VPC, ventricular premature complex.

1 | INTRODUCTION

Exercise-induced cardiac remodeling as a consequence of long-term training is a well-known phenomenon in both humans and horses also referred to as *athlete's heart*.[1-5] In horses, the most pronounced changes are increased left ventricular (LV) internal diameter and LV muscle mass caused by eccentric hypertrophy.[3-5]

In humans, athlete's heart is further characterized by electrophysiological adaptations to training. Most essentially, athletes have lower resting heart rates (HR) and sinus bradycardia, compensating for the effect of a larger heart and the concomitant increase in stroke volume (SV).[6-8] In addition, invasive electrophysiological studies in athletes have identified prolongation of sinus node recovery time (SNRT), confirming training-induced sinoatrial nodal (SAN) adaptation.[9] Similar alteration is evident in the atrioventricular (AV) node, and prolonged PR interval and Mobitz type 1 (Wenckebach) second-degree atrioventricular block (2AVB) are common findings of the athletic heart ECG.[7,9-11]

Knowledge on exercise-induced ECG changes in horses is scarce. It has been suggested the trained horse has a slower HR and prolonged PR interval,[12-16] whereas other studies failed to support these findings.[17-20] The disparity may be explained by small study populations, immature animals and lack of control groups in the different studies.[12-20] Atrioventricular nodal conduction in horses is different from that of humans and 2AVB is a common finding, reported to occur in up to 40% of horses.[21] Furthermore, it is unclear whether the definitions of Mobitz type 1 (Wenckebach) and Mobitz type 2 2AVB derived from human medicine are directly applicable to equine cardiology.[22,23] To our knowledge, a single study, conducted in our laboratory, evaluated the effect of training on 2AVB in a small group of horses, where a difference between trained and untrained horses was not identified and the types of 2AVB were not classified. However, in this study the trained horses had longer PR intervals, which supported altered AV conduction, possibly caused by intrinsic remodeling within the AV node.[16]

In humans, recordings of the specialized conduction system of the heart including SNRT, AV, and His bundle recordings commonly are used to assess conduction abnormalities.[24-26] In horses, SNRT and His bundle recordings are described infrequently.[27-29] However, with the emerging possibility of invasive electrophysiological studies and mapping procedures, these types of recordings have great potential to identify the mechanisms of SAN and AV conduction and possibly the effect of training in horses.

We aimed to investigate the effect of training on resting HR and ECG parameters, including assessment of resting arrhythmia burden in Standardbred trotters. To examine if SAN and AV nodal function was affected by training, we obtained recordings of SNRT and His intervals.

2 | MATERIAL AND METHODS

2.1 | Animals

The ECG recordings were collected from trained and untrained Standardbred trotters from 18 different stables, where the following predefined criteria were required for inclusion:

Trained horses included in the study had been subjected to training for at least 3 years. Furthermore, the horses had a racing career, up until the beginning of the study, spanning at least 3 consecutive years or 4 years in total if an injury prevented the horse from racing in a given year. Training routines can be found in the Data S1.

Untrained horses had not been trained for at least 1 year and had not competed within 4 years before the study. These horses were turned out into paddocks daily, allowing them to have some light activity but no forced training. Only clinically healthy horses ≥5 years of age were included. Horses with cardiac murmurs of grade ≤ 3/6 were accepted.

In addition to the 18 stables (211 horses) that participated in the study, ECGs from 10 horses[30-32] and another 32 horses (unpublished) that had been enrolled in previous cardiovascular studies in our laboratory were included. Thirteen (6 untrained and 7 trained; mean age, 7.7 ± 2.5 years; mean weight, 486 ± 57 kg) were included in a separate study involving invasive electrophysiology (EP) in which recordings of His bundle signals could be obtained along with SNRT recordings. Further information on the horses from previous studies that were enrolled in the current study can be found in Table S1.

The invasive EP experiment was authorized by the Danish Animal Inspectorate (license number 2016-15-0201-01128). The study was approved by the local ethical committee at the Department of Veterinary Clinical Sciences, University of Copenhagen. The study was performed in accordance with the European Commission Directive 2010/63/EU. Written consent was obtained from owners before inclusion of the horses.

2.2 | ECG recordings

A 3-lead modified base-apex ECG was recorded using Televet100 or Televet101 (KRUTECH Televet, Kruuse A/S, Maarslev, Denmark) with 2 separate channels and bipolar leads at a sampling rate of 500 Hz as previously described.[33] Electrode placement is illustrated in Figure 1. A 2-hour ECG was recorded in the afternoon or evening while the horses were at rest in their stables. We analyzed 24-hour resting ECG recordings from the 32 horses (18 trained and 14 untrained) in our existing database (Table S1). From these horses, the 2-hour recordings were blindly selected from the 24-hour ECG recording. The 2 hours were randomly chosen from a time point during the afternoon or evening (4-9 pm).

2.3 | ECG analysis

After quality control, the ECG recordings were analyzed using Televet100 analysis software (Version 6.2.0. Engel Engineering Service GmbH, Heusenstamm, Germany), which enabled marking of RR intervals with deviation >20% from previous RR intervals. The RR analysis assisted in manual detection of the following arrhythmias:

Sinus pause (RR interval ≥ 20% longer than the normal RR interval, but shorter than the sum of 2 normal RR intervals), sinus block

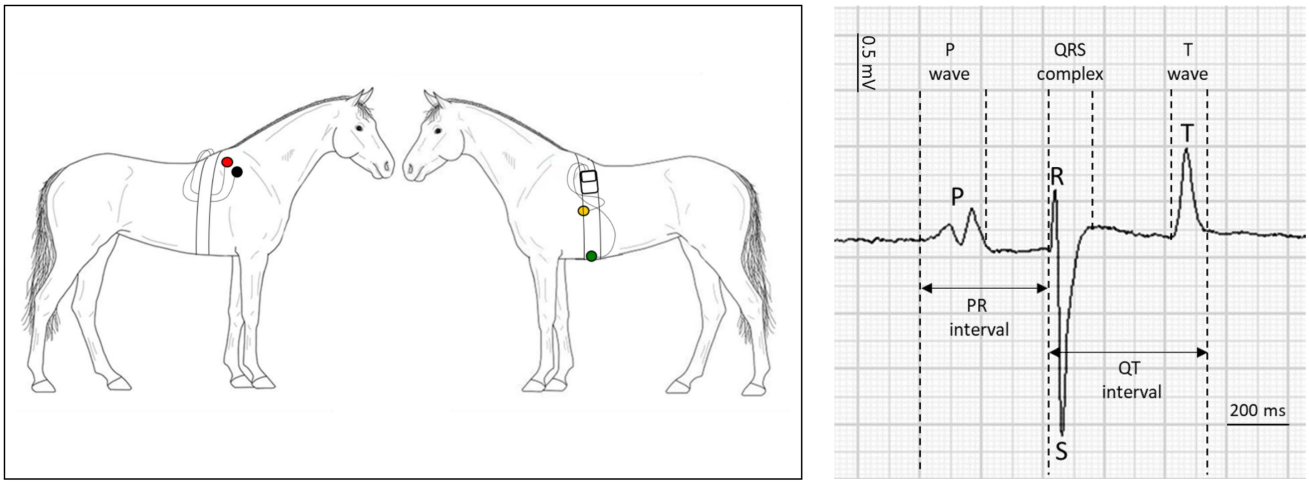

FIGURE 1 Electrode placement and outline of the measured ECG parameters. *Left*: Electrode placement: The negative red electrode was positioned on the right scapula; the positive green electrode was placed caudal to the xiphoid process approximately 10 cm left to the midline. The yellow positive electrode was placed caudal to the long head of M. triceps between the 6th and 7th rib in a horizontal line from the Art. humeri and the black electrode (neutral) was placed next to the red electrode but can be placed anywhere. *Right*: Measured ECG parameters: The P wave duration, PR interval QRS duration, T wave duration and QT interval were measured in a 10-second recording strip at paper speed 100 mm/s and amplitude 20 mm/mV in lead II. The analysis was conducted off line by 2 operators blinded to training status using televet100 and the analyzer tool Cardio Calipers (Version 3.3. Iconico, New York)

(RR interval equal to the sum of 2 normal RR intervals), sinus arrest (RR interval longer than the sum of 2 normal RR intervals), second-degree AV block (2AVB), atrial premature complexes (APC), and ventricular premature complexes (VPCs) according to predefined definitions.[34] For representative examples, see Figure S1. Bradycardia was defined as HR < 26 bpm.[35]

Ten seconds (typically 5-7 heart beats) during which the horse had its lowest HR in the absence of arrhythmias were chosen for resting HR determination and evaluation of P wave duration, PR interval, QRS duration, QT interval, and T wave duration using a paper speed of 100 mm/s and gain of 20 mm/mV in lead II (Figure 1). The analysis was conducted by 2 operators blinded to training status using Televet100 and the analyzer tool Cardio Calipers (Version 3.3. Iconico, New York). Interobserver and intraobserver coefficients can be found in Table S2. The P wave and T wave morphology was classified as either monophasic, biphasic, or bifid. Representative examples are presented in Figure S2.

2.4 | His recordings

His recordings were obtained from the right atrium (RA) during a 3-dimensional (3D) electroanatomical mapping procedure performed on standing sedated horses as previously described.[36,37] During the procedure, all horses were kept sedated using a standardized protocol including continuous rate infusion of 180-360 mL/h of 1.0 mg/mL xylazine (Xysol Vet 20 mg/mL, ScanVet Animal Health A/S, Fredensborg, Denmark). Additional details on the sedation protocol can be found in the Data S1 along with the duration of the procedures. An 8 Fr and an 11 Fr sheath (Introducer Sheath, Fr. 8/11. Terumo Medical Corp., 950 Elkton, MD 21921 USA) were placed in the left jugular vein from where a 16 polar electrode Advisor HD Grid Sensor Enabled Mapping Catheter (Abbott Medical, St Paul, MN, spacing 3 mm) was introduced into the right atrium along with a steerable decapolar diagnostic catheter (Livewire, Abbott Medical, spacing 2-5-2 mm). A surface ECG placed as specified in a previous study[36] along with the catheters were connected to an EnSite Velocity (Abbott Medical A/S, USA) 3D electroanatomical cardiac mapping system. Another 12-lead surface ECG[38] was placed and connected to Workmate (EP-Workmate Recording System V.4.3.2, Abbott Medical A/S, USA), allowing simultaneous ECG and intra-atrial bipolar electrogram (EGM) recordings using the following settings: ECG signal sampling rate 2000 Hz, Notch filter 50 Hz, and high/low bandpass filter 30/300 Hz for mapping catheter signals.

For His bundle recordings, the decapolar catheter, which resembles the routinely used standard quadripolar catheter used for His recordings in humans, was advanced into the septal part of tricuspid annulus in the right atrium, guided by the anatomical maps. Here, stable multichannel recordings, including atrial and ventricular EGM signals, were obtained while the horses were in sinus rhythm. If stable signals could not be obtained using the decapolar catheter, the HD grid catheter was used, enabling more stable recordings. Only signals with clear atrial and ventricular EGMs were considered for analysis such that a clinical cardiologist experienced and specialized in electrophysiology of humans (PS, DL) confirmed the region to be relevant for His signal recordings guided by atrial mapping. The following were required for a His measurement to be included in the analysis: (a) intrinsic sinus depolarization, (b) clear A and V signals with a steep deflection in between, easily distinguishable from the baseline, present in 3 consecutive beats, (c) recording of the signal at the

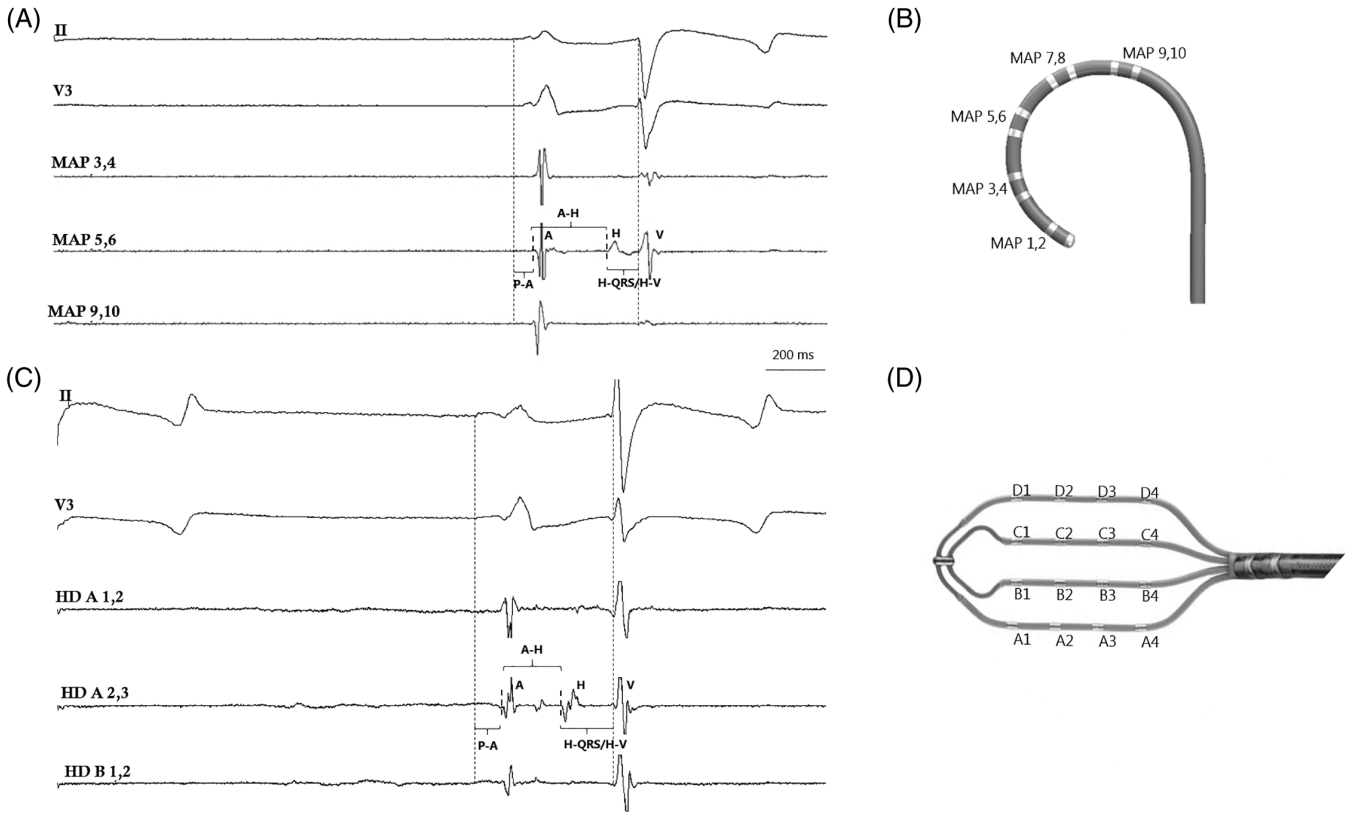

FIGURE 2 Intra-atrial His recordings. Two representatives of atrioventricular conduction intervals. (A) Representative of His signals (H) recorded with the decapolar catheter which is illustrated in (B). *From top to bottom*: Surface lead ECG II and V3 (optimized for P waves) followed by 3 interpolar channels reflecting the local recording obtaining the His signal (MAP 5,6) along with 2 channels too remote to obtain the His signal (MAP 3,4 and MAP 9,10). This emphasizes that the catheter needs to be placed very closely to the area of the AV node/His bundle in order to obtain the His signals. (C) Representative of His signals recorded with the HD grid which is illustrated in (D), including the channel close enough to the AV node (HD A 2,3) and 2 examples of channels too remote from the AV node (HD A1,2 and HD B1,2). For both (A) and (C): Long vertical dotted lines outlines the beginning of P wave and the QRS complex on surface ECG. Short vertical dotted lines outline the beginning of atrial (A) electrogram (EGM) and His EGM (H). Measurements were conducted for P-A: from P wave (P) to A, for A-H: from A to His and for H-V: from His to ventricular EGM (V). Intervals were measured when the His signal was visible in 3 consecutive beats at paper speed 125 mm/sec, amplitude 0.2 V/cm for electrograms and 0.5 V/cm for ECG. Signals were recorded using Workmate at signal sampling rate 2000 Hz, Notch filter 50 Hz and with High/Low bandpass filter 30/300 Hz for catheter and grid signals. Representatives are here shown in paper speed 100 mm/s

anatomical location of the distal AV node region confirmed by the electroanatomical map of the right atrium, and (d) minimal noise. Two His recording intervals were measured from each horse. Measurements of the obtained signals were performed offline in Workmate using build-in analysis tools at paper speed 125 mm/s. Amplitude was 0.2 V/cm for EGMs and 0.5 V/cm for ECG.

The following intervals were measured according to guidelines used in humans[24,39] and representative recordings are given in Figure 2: P-A interval reflecting the conduction time through the atria, which is defined as the interval from the beginning of the P wave on the surface ECG to the atrial EGM recorded from the intra-atrial catheter, A-H interval reflecting the conduction time through the AV node defined as the interval from the atrial EGM to the His signal EGM from the intra-atrial catheter, along with H-V interval reflecting the conduction time from the His bundle to the ventricular myocardium defined by the interval between the His signal EGM and the beginning of the ventricular EGM measured from the intra-atrial catheter, respectively.

2.5 | SNRT

In all horses, SNRT was measured during continuous rate infusion of sedation just before His recordings. The catheter was slowly advanced through the cranial vena cava to the cranial part of the right atrium. The goal was to achieve a location with a maximal early activation time at the onset of the P wave in the surface ECG (activation time mapping) during sinus rhythm and a paced P wave, which resulted in a P wave morphology in the surface ECG comparable to the P wave during sinus rhythm (pace-mapping). Using the intra-atrial catheter, the RA was paced for 30 seconds at pacing cycle length (PCL) 800, 600, and 400 ms at 2 times threshold at pulse width 2 ms. The SNRT was determined as the time between the last paced stimulation and the first spontaneous atrial depolarization (Figure 3). The SNRT was measured 2 times after an approximately 1-minute rest period after each pacing period.

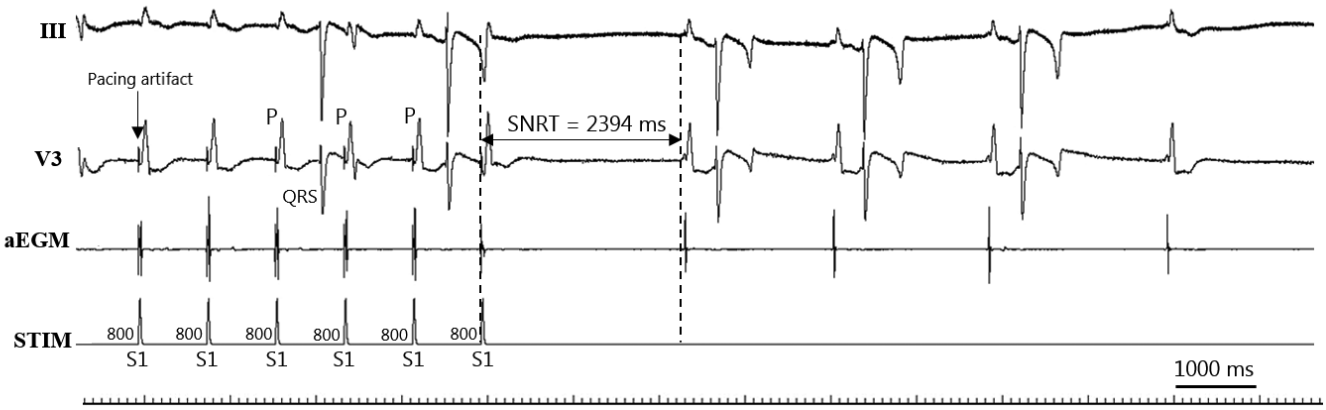

FIGURE 3 Sinus node recovery time (SNRT). Representative of a SNRT recording. From top to bottom: Surface ECG lead II and V3 (optimized for P waves), right atrial electrogram (aEGM), and stimulation channel (STIM). Pacing with 800 ms (S1) from the right atrium was performed for 30 seconds followed by 1-minute pause. The SNRT (outlined by dotted vertical lines) was defined as the interval between the last pacing spike to the beginning of the first sinus complex (P wave). Vertical arrow points out pacing artifact, which can be visible on the surface ECG just before the P wave (P). PCL, pacing cycle length

2.6 | Statistical analysis

For statistical analysis, GraphPad Prism ed.8 (GraphPad Software, USA) and R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) were used. The data were assessed for normality by visual inspection of histograms and by use of the Shapiro-Wilk test. Data are presented as mean ± SD unless stated otherwise. An unpaired *t*-test was conducted to compare age between trained and untrained horses. The ECG parameters from trained and untrained horses were compared using multiple regression models. The models for HR and the corrected QT (QTc) were adjusted for sex and age, and for the remaining ECG parameters, adjustments for sex, age, and HR were implemented. To account for the non-linear relationship between the QT interval and HR, QTc was calculated based on the piecewise linear regression model appropriate for Standardbred racehorses.[40,41] We also assessed the effect of age and sex on ECG variables. Testing for interaction between training status and age or sex was done to assess if the effect of training differed across age and sex (effect modification). The occurrences of arrhythmias in trained and untrained horses were assessed using logistic regression models with adjustment for age and sex to obtain odds ratios (OR). A similar procedure was performed for T wave morphologies having binominal outcomes, whereas P wave morphology had multinominal outcomes, and a Fisher's exact test was conducted. For SNRT, a mixed effects analysis was performed, where PCL was fixed and horses were random effects. A 2-sided *P*-value <.05 was considered significant. Only descriptive statistics were performed on the His signal recordings because of a low number of horses in the untrained group.

3 | RESULTS

3.1 | Study population

Electrocardiograms were collected from 201 trained and 52 untrained Standardbred trotters (mean age trained, 6.6 ± 2 years vs untrained, 11.7 ± 4 years; $P < .001$). Five trained horses were excluded from the ECG parameter analysis because of a large arrhythmia burden that prevented identification of 5-7 consecutive beats at low HRs without arrhythmias; these horses remained in the arrhythmia classification study.

The untrained group consisted of 44 mares (85%), 7 geldings (13%), and 1 stallion (2%); and the trained group consisted of 65 mares (32%), 113 geldings (56%), and 23 stallions (12%).

3.2 | ECG parameters

The mean ± SD of ECG parameters with *P*-values for adjusted and unadjusted comparisons are shown in Table 1. Heart rate was lower in the trained group both before and after adjusting for sex and age ($P = .001$). Also, QTc was shorter in the trained horses before and after adjusting for sex and age ($P = .04$) whereas P wave duration and QRS duration was prolonged in the trained group only for the unadjusted values. Mares had shorter P wave durations than geldings and stallions ($P = .04$), stallions had shorter PR intervals ($P < .001$), and longer QRS durations ($P = .01$) compared to geldings. The PR interval increased with age ($P = .05$). The 95% reference intervals for the ECG parameters based on the data from all of the horses are presented in Table 1.

3.3 | Arrhythmia burden and P and T wave morphologies

The most frequent arrhythmias were sinus pauses, sinus arrhythmia, 2AVB and APCs, whereas sinus arrest and sinus blocks were less frequently detected. The number of horses exhibiting these arrhythmias is summarized in Table 2. Ventricular premature complexes only were detected in trained horses, of which 1 exhibited >70 VPCs during the

TABLE 1 Resting ECG parameters from untrained and trained horses

ECG parameter	Untrained (n = 52) (mean ± SD)	Trained (n = 196) (mean ± SD)	Unadjusted *P*-value	Adjusted difference (mean ± SE)	Adjusted *P*-value	95% reference interval
Heart rate (bpm)	32.9 ± 4.2	30.8 ± 2.6	<.001†	−2.1 ± 0.7	.001*	[26-39]
P wave duration (ms)	155.6 ± 19.6	162.4 ± 19.1	.04*	7.2 ± 4.3	.1	[119-200]
PR interval (ms	381.5 ± 57.0	389.4 ± 53.7	.35	18.3 ± 11.6	.11	[283-493]
QRS duration (ms)	124.2 ± 9.5	129.4 ± 10.8	.002**	3.4 ± 2.3	.15	[109-149]
QT interval (ms)	520.9 ± 31.9	513.8 ± 26.9	.1	−4.3 ± 6.1	.47	[462;571]
QTc interval (ms)	531.0 ± 27.1	516.0 ± 27.4	<.001***	−12.2 ± 5.9	.04*	[463; 574]
T wave duration (ms)	140.8 ± 25.0	142.2 ± 24.7	.72	−4.4 ± 5.5	.45	[94;188]

Note: Mean ± SD and *P*-values from the unadjusted and adjusted (age and sex) multiple regression models are presented along with the adjusted difference ± standard errors and calculated 95% reference intervals for all ECG parameters. These intervals may be considered normal values for adult Standardbred trotters.
Abbreviation: bpm, beats per minute.
*P < .05, **P < .01, ***P < .001, †P < .0001.

2-hour ECG recording. No horses had AF or atrial or ventricular tachycardia during the ECG recording.

Trained horses were more likely to exhibit 2AVB compared to untrained horses after adjusting for age and sex, where the OR of exhibiting 2AVB was 2.59 in the trained horses (P = .04). The prevalence of arrhythmias and OR in the 2 groups are presented in Table 2. Eighteen trained (15.5%) and 2 untrained (9.1%) horses exhibited 2AVB where 2 consecutive P waves were blocked. Stallions less often exhibited 2AVB than geldings and mares (P = .002). Both trained and untrained horses with 2AVB displayed considerable fluctuations in PR interval before block, which mostly did not comply with the traditional Wenckebach pattern known from human cardiology. A wide variety of PR interval patterns was observed. No cases of consistent PR interval before 2AVB (Mobitz type 2) were detected in either group. The effects of age and sex on the ECG parameters adjusted for training status are presented in Table 3. No interactions between age and training status or sex and training status were found for any ECG parameter.

Monophasic and biphasic T wave morphologies were present in both groups with a lower incidence of biphasic T waves in the trained group compared to the untrained group (OR, 0.24; P = .003). Most horses (>80%) had bifid P waves, and only a few horses had either monophasic or biphasic P waves and rarely, alternating between biphasic and bifid P waves (n = 2) in the 10-second recording with lowest HR (Table 2). No differences in different P wave morphologies were found between the 2 groups (P = .17).

An additional 24-hour ECG was recorded in 32 horses, and of those, 28 horses (87.5%) exhibited 2AVB (Table 4). Second-degree AV block was detected in only 20 (62.5%) of these horses during the 2-hour ECG recording otherwise used to assess arrhythmia burden. The 8 horses where no 2AVB was detected during the 2-hour recordings (7 untrained and 1 trained) experienced few instances of 2AVB during the 24-hour recording (median untrained, 32 2AVB/24 hour; range, 6-206; median trained, 1 2AVB/24 hour). The median number of ectopic beats during the 24-hour ECG recording was 1.5 (range, 0-8) for untrained horses and 1 (range, 0-11) in the trained horses. These numbers were even lower for VPC, with a median of 0 for both groups, ranging from 0 to 1 for untrained and from 0 to 31 for the trained group.

3.4 | His Signals and Sinus node recovery time

Recording of His signals was successful in 7 of 13 horses (2 untrained; geldings, mean age, 7.5 ± 1 years; 5 trained horses; 2 mares and 5 geldings, mean age, 7.8 ± 3 years). The mean P-A interval was 71 ± 20 ms, mean A-H was 209 ± 41 ms, and mean H-V interval was 134 ± 41 ms. The distribution of His intervals in trained vs untrained horses is summarized in Figure 4A and representative His signals can be found in Figure S3. The H-V interval varied in 5 out of 7 horses, whereas A-H fluctuated less and only varied in 2 out of 7 horses. The sum of the P-A, A-H, and H-V intervals is equal to the PR interval of which the mean ± SD was 382 ± 58 ms in untrained horses and 416 ± 52 ms in trained horses (Figure 4A).

The SNRT measurements were successful in all 13 horses, ranging from 1249 to 2616 ms in the untrained group and from 1611 to 2901 ms in the trained group. The largest difference in SNRT was found at PCL 800 ms, but was not significant (untrained: 1927 ± 360 ms vs trained: 2286 ± 309 ms; P = .09; Figure 4B).

Additionally, we obtained His recordings in the presence of spontaneous 2AVB in 1 of the horses (Horse 4). The horse exhibited 4 single 2AVB and 2 blocks in which 2 consecutive P waves were not followed by QRS complexes. Only those with 3 preceding conducted beats were measured and are presented in Figure 5 along with 1 more measurement. Preceding the 2AVB, the PR interval fluctuated with variable length, the A-H interval remained constant whereas the H-V interval varied.

TABLE 2 Prevalence of arrhythmia occurrence and T wave and P wave morphologies

			Unadjusted values		Adjusted values	
Arrhythmia	**Untrained (n = 52) (%)**	**Trained (n = 201) (%)**	**OR [95% CI]**	***P*-value**	**OR [95% CI]**	***P*-value**
Sinus pause	48.1	53.2	1.2 [0.7; 2.3]	.5	1.1 [0.4; 2.5]	.9
Sinus block	3.8	1.0	0.30 [0.03; 2.1]	.2	0.8 [0.03; 36.6]	.9
Sinus arrest	3.8	1.0	0.30 [0.03; 2.1]	.2	0.61 [0.04; 1.7]	.74
2AVB	42.3	48.3	1.27 [0.7; 2.49]	.44	2.59 [1.1; 6.5]	.04*
APC	15.4	20.9	1.45 [0.7; 2.5]	.38	1.43 [0.4; 4.9]	.54
VPC	0.0	3.5	NA	NA	NA	NA
Bradycardia	4.0	3.0	1.30 [0.2; 5.8]	.75	1.00 [0.1; 8.8]	>.99
Morphology	**Untrained (n = 52) (%)**	**Trained (n = 196) (%)**	**OR [95% CI]**	***P*-value**	**OR [95% CI]**	***P*-value**
T $wave_{Monophasic}$	34.6	60.7	-	-	-	-
T $wave_{Biphasic}$	65.4	39.3	0.34 [0.2; 0.6]	.001**	0.24 [0.1; 0.6]	.003**
P $wave_{Bifid}$[a]	80.8	89.8	-	.17[a]	-	-
P $wave_{Biphasic}$[a]	13.5	8.2	-		-	-
P $wave_{Bifid+biphasic}$[a]	1.9	0.5	-		-	-
P $wave_{Monophasic}$[a]	3.8	1.5	-		-	-

Note: Odds ratio (OR) and *P*-values for untrained and trained horses from both the unadjusted and adjusted (age and sex) logistic regression models are presented.
Abbreviations: 2AVB, second-degree AV block; APC, atrial premature complexes; NA, not available; VPCs, ventricular premature complexes.
[a]Multinominal data analyzed using Fischer's exact.
*$P < .05$, **$P < .01$.

TABLE 3 The effect of age and sex on ECG parameters

	Age effect, per year (*P*-value)	Age-training interaction (*P*-value)	Mare effect vs. gelding (*P*-value)	Stallion effect vs. gelding (*P*-value)	Sex-training interaction (*P*-value)
HR (bpm)	0.03 (.73)	.78	−0.04 (.93)	0.18 (.78)	.24
P wave duration (ms)	0.64 (.19)	.84	−5.94 (.04)*	−1.02 (.81)	.76
PR interval (ms)	2.65 (.05)*	.66	−9.31 (.22)	−59.42 (<.001)***	.80
QRS duration (ms)	0.04 (.87)	.61	−2.88 (.06)	7.04 (.003)**	.61
QT interval (ms)	1.09 (.12)	.67	−6.40 (.12)	−5.75 (.36)	.72
T wave duration (ms)	−0.21 (.73)	.44	−4.45 (.22)	8.85 (.11)	.46
Sinus pause	−0.07 (.16)	.99	0.30 (.31)	−0.60 (.20)	.70
Sinus block	0.10 (.53)	.71	17.69 (.99)	18.37 (.99)	.76
Sinus arrest	0.07 (.65)	NA	0.84 (.52)	−14.81 (.99)	.88
2AVB	0.07 (.21)	.07	0.40 (.18)	−2.37 (.002)**	.66
APC	0.04 (.53)	.47	−0.34 (.37)	0.40 (.43)	.09
Bradycardia	0.03 (.84)	.32	0.34 (.69)	0.49 (.98)	.75

Note: Statistical analysis including linear and logistic regression models investigating the age and sex effect adjusted for training status and to identify possible interactions.
Abbreviations: 2AVB, aecond-degree AV block; APC, atrial premature complexes; HR, heart rate; NA, not available.
*$P < .05$, **$P < .01$, ***$P < .001$.

4 | DISCUSSION

We investigated the effect of long-term exercise on basic electrophysiological parameters of the heart in Standardbred horses. The main findings are decreased HR (by 2 beats per minute) and increased occurrence of 2AVB in trained Standardbred racehorses compared to untrained horses. We also gained new insights into AV nodal conduction in horses, reporting on the AV and His intervals and showing that conduction block distal to the His bundle can occur in horses with 2AVB.

TABLE 4 Prevalence of untrained and trained horses exhibiting arrhythmias analyzed from both 2-hour and 24-hour ECG recordings

	Untrained (n = 14)		Trained (n = 18)	
Arrhythmia	**2 hours, n (%)**	**24 hours, n (%)**	**2 hours, n (%)**	**24 hours, n (%)**
Sinus pause	10 (71.4)	11 (78.6)	11 (61.1)	17 (94.4)
Sinus block	0 (0)	1 (7.1)	0 (0)	1 (5.6)
Sinus arrest	0 (0)	4 (21.4)	0 (0)	1 (5.6)
2AVB	5 (35.7)	12 (85.7)	15 (83.3)	16 (88.9)
APC	2 (14.2)	8 (57.1)	6 (33.3)	12 (66.7)
VPC	0 (0)	3 (21.4)	0 (0)	5 (27.8)
Bradycardia	0 (0)	4 (28.6)	2 (16.7)	6 (33.3)

Abbreviations: 2AVB, second-degree AV block; APC, atrial premature complexes; n, number of horses presenting with the arrhythmia; VPCs: Ventricular premature complexes.

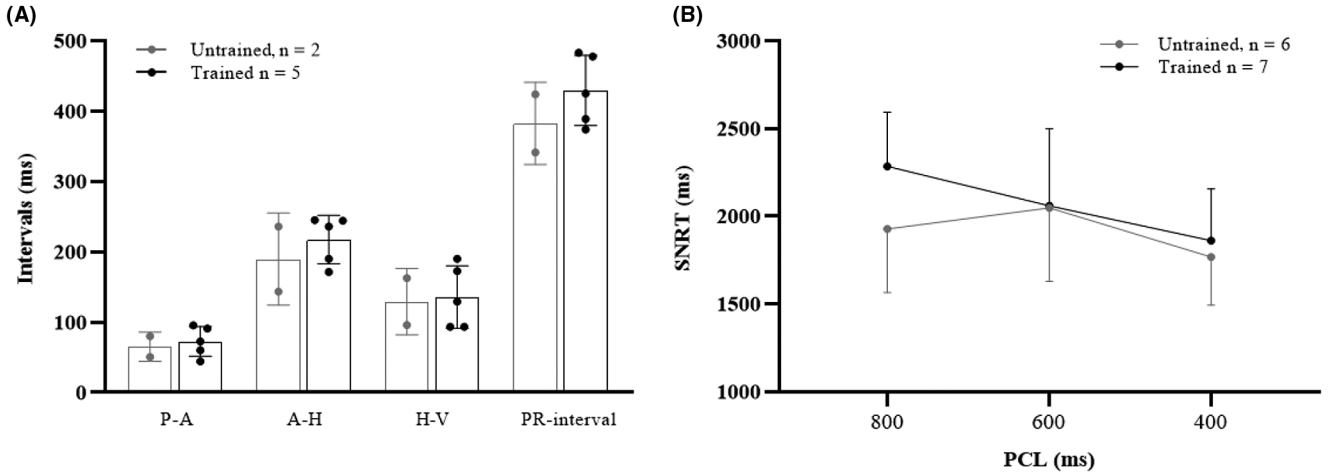

FIGURE 4 (A) Atrioventricular conduction intervals and (B) sinus node recovery time (SNRT) from trained and untrained Standardbred horses. Values are mean ± SD. **P-A**: P wave to atrial electrogram (EGM); **A-H**: atrial EGM to His EGM; **H-V**: His EGM to ventricular EGM. PCL, pacing cycle length. One missing value in SNRT PCL 400 ms in the trained group

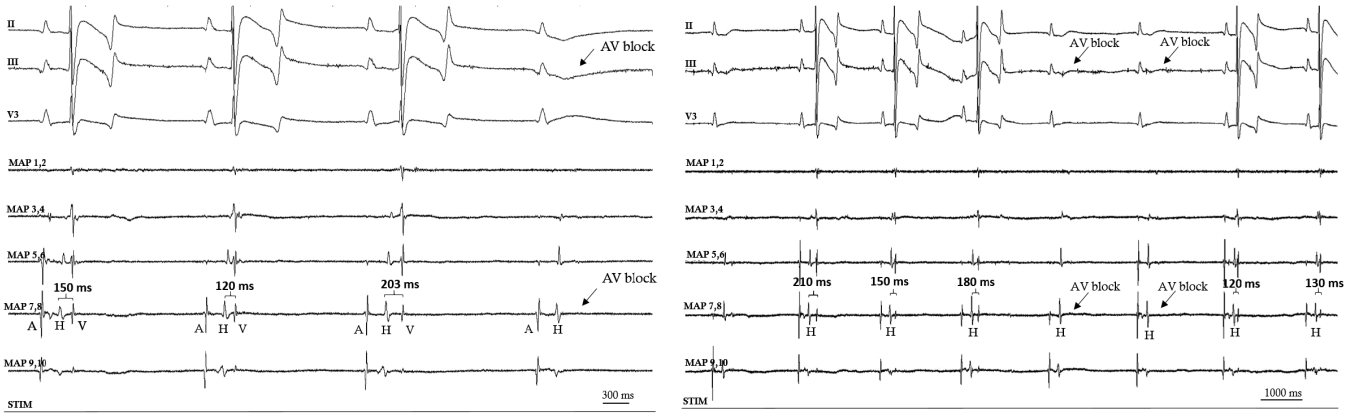

FIGURE 5 Intra-atrial His recordings from 1 horse exhibiting second-degree atrioventricular block. *Left*: Single atrioventricular (AV) block. *Right*: Two consecutive atrioventricular blocks. The H-V interval varied toward the atrioventricular block in both cases. Amplitude 0.2 V/cm for electrograms and 0.5 V/cm for ECG. *From top to bottom in both cases*: Surface lead ECG II and V3 followed by decapolar catheter channels (MAP) including stimulation channel (STIM). MAP 7,8 captured the His (H) signals and the atrial (A) and ventricular (V) electrograms. Signals were recorded using Workmate at signal sampling rate 2000 Hz, Notch filter 50 Hz and with high/low bandpass filter 30/300 Hz for mapping catheter. Arrows indicate the second-degree AV block. The duration of the H-V intervals is annotated to illustrate the variation in this interval around the second-degree AV block (black arrows)

4.1 | Effect of training on resting heart rate

The trained horses had lower resting HR compared to the untrained. Lower resting HR is a hallmark of the athletic heart and is well-recognized in humans. A decrease in HR in horses has been observed after 7 months of training.[14,15] These studies only included 2-year old Thoroughbreds with no untrained control group, and aging alone in these immature animals may have been responsible for the decrease in HR, leaving the training effect unanswered. Studies including mature horses also reported a decrease in HR in trained horses, but only few horses were included (<12 horses in each group)[12,13,16] and finally others were not able to identify a training-induced decrease in HR.[17-20] Given the subtle decreases observed in our study, horses may not alter their resting HR as much in response to training as do other mammals, including humans.[7,11,42,43] The reason for this difference is unknown, but the fact that horses already have very low resting HRs (approximately 35 bpm) may explain the low relative change (7% change) in HR as opposed to approximately 30% in human athletes.[2] Our study further investigated the function of the SAN by assessing SNRT. This parameter has been shown to be prolonged in human athletes, and resembles sick sinus syndrome.[9] We were not able to show a significant prolongation in SNRT in the trained horses but it was slightly longer at PCL 800 ms. Given the modest changes in HR, changes in the SNRT therefore would be subtle as well. Also, many horses exhibit wandering early activation during sinus rhythm,[44] which could result in a shift of the earliest activation site when SAN activity is suppressed by rapid pacing. Some of the horses did undergo changes in P wave morphology in the first beat after pacing, in which case a new pacing site was found. However, the role of different pacemaker sites within the atria must be explored further to understand the SNRT in horses. Finally, alpha-2 agonists including xylazine are known to decrease HR in horses[45] and have further been shown to prolong SNRT in humans,[46] but not in pigs.[47] All SNRT and His recordings were performed during continuous rate infusion of xylazine in all horses. Whether sedation with xylazine influences the SNRT, AV conduction and His conduction in horses warrant further systematic investigation, but was beyond the scope of our study.

The decrease in HR in human athletes is believed to be a physiological adaptation in response to repeated bouts of exercise inducing cardiac enlargement and increased SV.[1,48,49] The mechanism responsible for the decrease in HR has been proposed to be related to an increase in vagal tone, whereas recent studies reject this assertion and suggest that the reason for the decrease must be found within the SAN itself.[42,50,51] In horses, the mechanism is unexplored. However, a single study did observe a decreased intrinsic HR caused by training in young adult horses, but not in older horses, suggesting a local alteration within the SAN itself.[13]

Bradycardia is strongly associated with training in humans.[11,52-54] However, we did not observe an increased incidence of bradycardia in the trained horses because bradycardia was present in almost 30% of horses (during 24-hour ECG recording) regardless of training status. Older age was associated with an increased risk of bradycardia in the 24-hour ECG analysis (data not shown), and the cumulative effect of training and increasing age should be investigated.

4.2 | Effect of training on atrioventricular conduction in horses

In our study, training was associated with a higher occurrence of 2AVB in the trained horses. Almost half of the trained horses exhibited 2AVB during the 2-hour ECG recording, increasing to almost 90% of trained horses during a 24-hour ECG recording, identifying a much higher prevalence than previously reported.[21] Approximately 40% of horses in general exhibit 2AVB,[21] but another study identified 2AVB in 16.5% of horses based only on 10-minute ECG recordings.[22] Along with our results, this finding could indicate a higher prevalence of 2AVB than previously assumed. Exercise-induced 2AVB has been suggested to be caused by an increase in vagal tone or by intrinsic remodeling of key pacemaker ion channels in the AV node.[9,55] In horses, complete pharmacological block of the autonomic nervous system abolishes 2AVB[16,56] but when investigating the PR interval and Wenckebach cycle length (a measure of AV nodal refractoriness), these 2 parameters have shown to be persistently longer in horses exhibiting 2AVB compared to horses without 2AVB.[56] In parallel, we previously documented prolongation of the PR interval that persisted in trained horses compared to untrained horses after simultaneous pharmacological blockage of both the sympathetic and parasympathetic nervous systems.[16] Also we identified down-regulation of important pacemaker ion channels, including the hyperpolarization-activated cyclic nucleotide-gated channel 4 (HCN4) and the L-type calcium channels (Cav1.2) within the AV node in trained horses, which could be responsible for the slowed AV conduction seen in both human and equine athletes.[16]

4.3 | His signal recordings

In human medicine, His signal recordings are essential to understand arrhythmias involving the AV node, the His-Purkinje system or both, such as supraventricular reentry tachycardia, wide QRS complex tachycardia or 2AVB.[24] Recently, His recordings were obtained from the LV in 5 horses and from the right ventricle in 1 horse during general anesthesia.[28] In humans, His signals can be recorded from both the right and left side of the heart,[57] which also has been shown to be possible in horses.[28] This study included a thorough description of endocardial electroanatomical mapping in horses, unfortunately not specifying the duration of the obtained His intervals, preventing comparison with our findings.[28] However, a review from 2004 exploring allometric scaling among different animal species in regard to AV nodal conduction reported on P-A, A-H, and H-V intervals obtained from horses.[29] In this study, the average H-V duration in horses was reported to be 84 ms, which is shorter than the H-V intervals measured in our study. This difference might be explained by individual differences and the effect of a different sedation protocol.[29] We were

not able to explore the training effect of AV nodal conduction via His recordings because of the low number of successful His recordings in the untrained horses and further studies are warranted to clarify the effect of training on His intervals.

In horses, both gradual prolongation and fluctuating PR interval before AV block reflecting Mobitz type 1 (Wenckebach) AV block and constant PR intervals before AV block reflecting Mobitz type 2 2AVB have been described.[22,23,58,59] Whether the blocks originate in the AV node/supra-His (usually Mobitz type 1) or inside or below the His bundle region/infra-His (Mobitz type 2) has not yet been investigated in horses. Surprisingly, in our study, 1 horse experienced a delay in conduction or conduction block distal to the His bundle. This event occurred while the horse experienced decremental properties of the H-V interval and presence of the H signal during the 2AVB. Considering the low number of observations in our study and the fact that the horses were sedated, it remains unclear at which level of the conduction system the block exactly occurs in horses. However, these findings support the observations made by others that suggested that 2AVB in horses most likely is physiological, but yet different from what is described in humans exhibiting Mobitz type 1 2AVB.[22]

4.4 | Effect of training on QTc and T wave morphology

Previously it has been shown that the QT interval is prolonged in trained horses similar to findings in human athletes.[12,54] We, on the contrary, observed a shortening of the QTc in the trained horses that mostly had monophasic positive T wave deflections whereas the untrained horses primarily had biphasic T waves. Changes in ventricular repolarization also have been shown to occur in human athletes,[60] and further investigation in horses is warranted.

4.5 | Arrhythmias

Training did not increase the risk of APCs and VPCs in horses. In humans, ventricular arrhythmias have been proposed to be likely to occur as vigorous exercise increases chamber pressures, which may lead to a higher burden of stretch-related premature beats.[61] Studies exploring the mechanistic background of training-induced arrhythmias in other animal species suggest that increased cardiac dimensions, changes in vagal tone along with increased inflammation, and fibrotic development could favor atrial and ventricular arrhythmias as a result of training.[62,63] Few VPCs were detected in our study, and the incidence was higher among the trained horses. In fact, 2 trained horses exhibited 50-70 VPCs, which should prompt further evaluations.[64]

5 | LIMITATIONS

Our study had some limitations. Despite adjusting for age and sex, it would have been more appropriate to have used sex, body weight, and age-matched groups. Because RR intervals and not PP intervals were used to detect arrhythmias, misdiagnosis of sinus pauses may have occurred, because simple variations in PR interval may contribute to the diagnosis. Automatic analysis of the ECG parameters has several advantages over manual analysis, but software has not been developed for use on horse ECGs. Operators were blinded to the training status of the horses and were able to perform ECG analysis with high interobserver and intraobserver agreement, confirming acceptable consistency. Furthermore, some of the untrained horses had previously been trained and raced, which may be considered a limitation of the study because the potential training-induced remodeling may not have been completely reversed by the time of inclusion. Finally, the horses were sedated during the invasive EP recordings because the procedures were long and required the horses to move as little as possible. Sedation may, however, have an impact on both the sinus node and conduction through the AV node.[65]

6 | CONCLUSION

Analysis of resting ECG recordings from 253 Standardbred trotters identified a decrease in HR along with a higher risk of exhibiting 2AVB in trained horses compared to untrained horses. Furthermore, more trained horses had monophasic T waves, suggesting that training may alter ventricular repolarization. The function of specialized conduction was further explored using SNRT and His recordings. Training did not alter SNRT, and the effect on His intervals remains to be clarified. Training is believed to be the main influencer of the difference in HR and numbers of 2AVB, however, we cannot exclude age and sex effects on SAN and AV nodal function. Surprisingly, horses had much variation in H-V interval, as distinct from humans.

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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

The invasive EP experiment was authorized by the Danish Animal Inspectorate (license number 2016-15-0201-01128). The entire study was approved by the local ethical committee at the Department of Veterinary Clinical Sciences, University of Copenhagen. The study was performed in accordance with the European Commission Directive 2010/63/EU. Written consent was obtained from owners before inclusion of the horses.

HUMAN ETHICS APPROVAL DECLARATION

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

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