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Effect of induced chronic atrial fibrillation on exercise performance in Standardbred trotters

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Background: Atrial fibrillation (AF) is the most common arrhythmia affecting performance in horses. However, no previous studies have quantified the performance reduction in horses suffering from AF.

Objectives: To quantify the effect of AF on maximum velocity (V_{max}), maximum heart rate (HR_{max}), heart rate recovery (T_{100}), hematologic parameters and development of abnormal QRS complexes.

Animals: Nine Standardbred trotters.

Methods: Two-arm controlled trial. Six horses had AF induced by means of a pacemaker and 3 served as sham-operated controls. All horses were subjected to an exercise test to fatigue before (SET1) and after (SET2) 2 months of AF or sham. The V_{max} and HR_{max} were assessed using a linear mixed normal model. Abnormal QRS complexes were counted manually on surface ECGs.

Results: Atrial fibrillation resulted in a 1.56 m/sec decrease in V_{max} ($P < .0001$). In the AF group, $HR_{max} \pm SD$ increased from 226 ± 11 bpm at SET1 to 311 ± 27 bpm at SET 2. The AF group had higher HR_{max} at SET2 compared with controls ($P < .0001$), whereas no difference between the control and AF groups was observed at SET1 ($P = .96$). Several episodes of wide complex tachycardia were observed during exercise in 3 of the AF horses during SET2.

Conclusions and Clinical Importance: Atrial fibrillation resulted in a significant reduction in performance, an increase in HR and development of abnormal QRS complexes during exercise, which may be a risk factor for collapse or sudden cardiac death.

KEYWORDS

arrhythmia, atrial fibrillation, cardiology, exercise, heart rate, horse, performance

Abbreviations: BW, body weight; Ca^{2+} , calcium; CI, confidence interval; Cl^- , chloride; ECG, electrocardiogram; HR, heart rate; HR_{max} , maximum heart rate; K^+ , potassium; LA_{max} , maximum lactate concentration; Na^+ , sodium; PP, plasma protein; SET, standardized exercise test; SR, sinus rhythm; T_{100} , time in minutes until heart rate reach 100 bpm; V_{LA4} , velocity (m/sec) at lactate concentration of 4 mmol/L; V_{max} , maximum velocity (m/sec); VT, ventricular tachycardia; V_{200} , velocity (m/sec) at heart rate of 200 bpm.

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1 | INTRODUCTION

Atrial fibrillation (AF) is a detrimental arrhythmia in horses, and exercise intolerance is the most common complaint when affected horses are referred to the veterinarian.¹⁻³ The prevalence of AF in a mixed population of horses has been estimated at 0.3% to 2.5%,⁴⁻⁶ but can increase to 4% in predisposed breeds such as Standardbred trotters.⁷

The prevalence of AF has been estimated at 5.3% in middle-aged human athletes,⁸ and 0.3% in young athletes.⁹

During AF, no coordinated contraction of the atria occurs, and the patient must perform without atrial systole contributing to late ventricular filling.¹⁰ However, AF also results in other effects on cardiac hemodynamics, including a decreased end-diastolic pressure and volume in the ventricles, an increase in mean diastolic pressure in the atria and a decreased interval for passive diastolic filling in the event of tachycardia.^{10,11} For horses and humans in sinus rhythm (SR), the active contribution from the atria can account for approximately 10%-20% of ventricular stroke volume at rest,^{12,13} but the absent atrial pumping function in AF patients rarely clinically affects hemodynamic parameters at rest. However, the atrial pumping function becomes more important as the intensity of exercise increases, because the relative portion of passive filling is decreased because of tachycardia.¹⁴ A marked decrease in cardiac output therefore can be expected in AF patients during exercise and tachycardia.¹⁵

Previous studies have reported disproportional tachycardia in AF horses during exercise,^{3,16,17} and 1 study also reported a broadening of QRS complexes and abnormal ventricular activation.¹⁷ Furthermore, in horses with AF, increased pulmonary wedge pressure was observed during exercise, indicating increased left atrial pressure, most likely as a consequence of absent atrial systolic function.¹⁶ To date, no studies have quantified performance in horses with AF during high-intensity exercise.

The aim of our study therefore was to quantify the effect of AF on exercise performance and cardiac arrhythmias in Standardbred trotters during a treadmill exercise test to the point of fatigue, initially when horses were in SR and after 2 months of induced, chronic AF. We hypothesized that horses in AF would be unable to reach the same maximum velocity (V_{max}) compared with their own V_{max} in SR. Furthermore, we expected that the maximum heart rate (HR_{max}) would increase because of AF.

2 | MATERIALS AND METHODS

2.1 | Horses

Nine Standardbred trotter mares (aged 10.4 ± 4.7 years) were included in the study, with 3 of the horses serving as sham-operated controls. The horses all were retired racehorses, and before inclusion, they had been out of racing and training for a minimum of 2 months. During the study period, the horses were taken to the paddock daily (except for 3 weeks of box rest after pacemaker implantation), and no other physical training was allowed except for the treadmill exercise. The study was approved by the local ethical committee at the Department of Veterinary Clinical Sciences, University of Copenhagen and The Danish Animal Experiments Inspectorate (license number 2015-15-0201-00693) and was performed in accordance with the European Commission Directive 86/609/EEC.

2.2 | Clinical, cardiac, and lameness examination

The horses underwent a clinical examination including standard hematologic and biochemical blood testing before the study. A lameness

examination (including walking and trotting in a straight line and lunging on hard and soft surfaces) was conducted by 2 experienced veterinary surgeons (see acknowledgments). Based on this examination, a lameness score was given according to the American Association of Equine Practitioners lameness grading scale (score 0-5), and horses only were included in the study if the score was ≤ 2 , which was the case for all horses. A base-apex 24-hours Holter ECG (KRUTECH Televet, Kruuse A/S, Maarslev, Denmark) and a standardized echocardiographic examination (2-D, M-mode and color flow Doppler)¹⁸ were conducted using a portable ultrasound unit (Vivid I, GE Healthcare, Horten, Norway) with a phased array transducer (3S Phased Array transducer, GE Healthcare) and a simultaneous ECG recording. All horses had echocardiographic parameters within the reference interval, and only trivial valvular regurgitations were found. The clinical and cardiac examinations were performed by authors RB, HC, and EZH.

2.3 | Pacemaker implantation and induction of AF

Under local anesthesia and sedation, all 9 horses had dual-chamber pacemakers (Assurity MRI 2272, St Jude Medical Group, St. Paul, Minnesota) implanted via the right cephalic vein, with 2 leads (Tendril STS Pacing Leads 100 cm, St Jude Medical Group, St Paul, Minnesota) fixated (active fixation) in the right atrium to allow for tachypacing as previously described.¹⁹ After 3 weeks of recovery, AF was induced by intermittent burst pacing (600/min) in runs of 20 s. Once AF was self-sustained, the pacemaker was programmed to start tachypacing from both leads (each pacing at a rate of 170/min) if sensing an atrial rate < 170 /min. The next day, burst pacing was initiated again until self-sustained AF occurred and this approach was continued every day until AF remained self-sustained. The pacemaker remained off for horses in the control group. For horses in the AF group, the pacemaker was turned off permanently when the horses reached self-sustained AF of > 24 hours. The horses subsequently were auscultated daily to confirm presence of chronic AF.

2.4 | Standardized exercise treadmill test

The horses were weighed on a scale before each exercise test. Rectal temperature was measured before and immediately after cessation of each test.

The horses performed 2 standardized exercise tests (SET) on a high-speed treadmill (Säto, Knivsta, Sweden) at a room temperature of 21°C. The first test (SET1) was conducted before implantation of the pacemakers, and with all horses in SR. The second test (SET2) was performed 57-58 days after induction of AF for the 6 AF horses. At this time, the mean duration \pm SD of self-sustained AF was 38.5 ± 11.9 days (16.2, 36.0, 38.8, 46.1, 46.8, and 47.3 days of AF for each horse, respectively). The 3 control horses underwent a time-matched experimental protocol without AF induction, and SET2 was performed 57 days after the study start. The week before the first test, all horses were acclimatized to the treadmill at least 3 times with approximately 10 minutes of walking and trotting each time. The SET consisted of an incremental test to fatigue, with a warm-up period of 5 minutes of

walking (1.8–2.0 m/sec) and 5 minutes of trotting (4–5 m/sec) on a horizontal treadmill. At the end of the warm-up period, the treadmill was set to a 6% incline. The initial velocity was set to 6.5 m/sec for 6 horses (3 horses from the AF group and 3 control horses). Inadvertently, the remaining 3 horses from the AF group had the initial velocity set to 7 m/sec rather than 6.5 m/sec for both exercise tests. Because an unpaired *t*-test showed no significant difference between the number of steps, maximum heart rate (HR) or maximum lactate concentration for the 3 AF horses starting at 6.5 m/sec and those starting at 7 m/sec, the 2 groups were merged and the starting velocity was set to 6.5 m/sec for subsequent analyses for all horses. The velocity was increased by 0.5 m/sec every minute until the horse reached its limit of exercise tolerance, which was determined as the inability to maintain the running speed despite humane encouragement. The horses were walked for 30 minutes after the test before being returned to the stable. Two different observers were in charge of the treadmill velocity and deciding when the horses could not keep pace with the treadmill. The 2 observers were blinded concerning the maximum velocity (V_{\max}) test results of the individual horses from SET1 when performing SET2.

2.5 | Electrocardiographic recording

Electrocardiographic recordings were obtained with a base-apex ECG (KRUTECH Televet, Kruise A/S) as previously described.²⁰ Cardiac arrhythmias and HR were evaluated offline after the SET by an experienced observer using dedicated software (KRUTECH Televet, Kruise A/S). The HR was measured at rest, after 10 minutes of warm-up, during the last 15 seconds of each exercise step, and finally at 2, 5, 10, 15, 30, 60, and 120 minutes after the exercise test ended. The HR was calculated as a mean of the last 25 beats for each measurement point (HR_{mean}), and maximum HR was recorded (HR_{\max}) as the mean of the last 25 beats when horses were running at V_{\max} . Abnormal QRS complexes were categorized manually. If the QRS complexes had abnormal morphology or exhibited R-on-T morphology compared with the other beats, they were categorized as abnormal QRS complexes. If 2 abnormal QRS complexes occurred consecutively, these were categorized as couplets. If ≥ 3 occurred, these were categorized as wide complex tachycardia.²¹

2.6 | Blood samples

Blood samples were collected before, during and after the exercise test from a catheter in the jugular vein. Blood samples for measuring potassium (K^+), calcium (Ca^{2+}), sodium (Na^+), chloride (Cl^-), lactate, glucose, and plasma protein (PP) concentrations, packed cell volume (PCV) and pH were collected in heparinized 3 mL syringes at rest in the stable at the end of the 10 minutes warm-up period, during the last 15 seconds of each exercise step, immediately after the test, and at 2, 5, 10, 15, 30, 60, and 120 minutes after the SET ended. When a horse did not finish the full 60 seconds of the last exercise step, the blood sample was collected at the point when the horse could no longer keep pace with the treadmill. All blood samples were chilled and analyzed within 30 minutes using a blood gas analyzer (Radiometer ABL800,

Radiometer, Brønshøj, Denmark). Packed cell volume was measured in duplicate by centrifuging heparinized blood in a capillary tube using a microhematocrit reader (Microhematocrit Reader, Hawksley, Colorado), and PP was measured in duplicate by refractometry (Sur-NE Refractometer, Atago Inc, Bellevue, Washington).

2.7 | Statistical analysis

Maximum HR (HR_{\max}) during exercise, maximum lactate concentration (LA_{\max}), and the blood parameters K^+ , Ca^{2+} , Na^+ , Cl^- , lactate, glucose, PP, PCV, and pH at the last exercise step were modeled by a linear mixed normal model including fixed effects of SET, observer and intervention (AF or control group at SET1 or SET2). To account for heterogeneity among horses, a random effect of horse was included. The significance of fixed effects was assessed by F-tests. The maximum velocity (V_{\max}), velocity at a HR of 200 bpm (V_{200}), velocity at a lactate concentration of 4 mmol/L (V_{LA4}) and cardiac recovery time (which was the time in minutes until HR reached 100 bpm after the exercise test finished [T_{100}]) were modeled by an interval-grouped normal model including systematic effects of SET, observer and intervention (AF or control group at SET1 or SET2). To account for heterogeneity among horses, inference was performed using a robust independence working generalized estimating equation procedure. This model specification corresponded to an ordinary linear normal model for the actual values of speed and time, where we accounted for the fact that the actual values were not observed; rather, we only observed that they fell within prespecified intervals. The significance of effects was assessed by robust Wald tests.

Estimated SET-specific intervention effects and changes from SET1 to SET2 within the AF and control groups were reported with adjusted *P*-values and family wise 95% confidence intervals (CI) using the single-step correction for multiple testing. Goodness-of-fit was validated both graphically and numerically, assessing systematic departures in and normality of residuals and random effects estimates.

In all models, independence between residuals and predicted values was checked by residual plots and normality of residuals, and estimated random effects were checked by qq-plots and by the Shapiro Wilks test. No indications of model violation were seen in the residual plots. No substantial deviations from normality were seen in qq-plots.

Data are presented as mean \pm SD. *P*-values were evaluated at a 5% significance level. All analyses were performed using the statistical software R version 3.3.2 (The R Foundation for Statistical Computing, Vienna, Austria) with the add-on packages lmerTest,²² and multi-comp.²³ Graphs were produced using GraphPad Prism 7.0 (GraphPad Prism 7.0 software Inc, La Jolla, California).

3 | RESULTS

Body weight (BW) at inclusion in the study was 475 ± 47 kg. All horses gained weight and at the second exercise test, BW was 501 ± 44 kg ($P = .0039$). All horses completed both exercise tests. Rectal temperature for both groups increased after the tests, but we observed no evidence of an effect of intervention on either temperature or weight.

3.1 | Maximum velocity (V_{max})

The V_{max} for the control group at SET1 and SET2 was 10.10 ± 0.45 and 10.42 ± 0.45 m/sec, respectively. For the AF group, V_{max} was 10.33 ± 0.66 and 8.78 ± 0.66 m/sec for SET 1 and SET2, respectively. Changes in the V_{max} from SET1 to SET2 were found to be different between the AF group and the control group ($P = .007$). No significant difference was found between the control and AF groups at SET1 (difference, 0.25 m/sec; CI, -0.61 m/sec; 1.11 m/sec; $P = .76$). However, a difference in the V_{max} was observed between the 2 groups at SET2, where the AF group ran significantly slower compared with the control group (difference, -0.86 m/sec; CI, -1.17 m/sec; -0.55 m/sec; $P < .001$). A significant effect of observer was found for the difference in V_{max} between SET1 and SET2, which was estimated to be 1.17 m/sec higher when observer 2 was controlling the treadmill velocity ($P < .0001$). No systematic effect of observer was found for the remaining parameters.

For the AF group, the observer-adjusted decrease in velocity from SET 1 to SET 2 was estimated at 1.56 m/sec, (CI, 0.87 m/sec, 2.24 m/sec; $P < .0001$). For the control group, the observer-adjusted decrease in velocity from SET 1 to SET 2 was estimated at 0.45 m/sec (CI, -0.33 m/sec, 1.36 m/sec; $P = .31$).

3.2 | Maximum HR (HR_{max})

Heart rates during the 2 exercise tests are shown for the 2 groups of horses (Figure 1A,B). The HR_{max} for the control group at SET1 was

222 ± 10 bpm (range, 210–236 bpm), and at SET2, the HR_{max} was 223 ± 9 bpm (range, 215–235 bpm). For the AF group, the HR_{max} at SET1 was 226 ± 11 bpm (range, 207–242 bpm), and the HR_{max} at SET2 was 311 ± 27 bpm (range, 276–346 bpm). When measuring only 1 RR interval and finding the shortest during the tests, the maximum HR for the control group at SET1 was 223 ± 15 bpm (range, 210–240 bpm), and at SET2 226 ± 11 (range, 218–238). For the AF group, the individual maximum HR for SET1 was 240 ± 31 bpm (range, 210–300) and during SET2 it was 378 ± 26 bpm (range, 337–492 bpm) for the AF horses. However, only the HR_{mean} was used for the statistical analyses. The change in HR_{max} from SET1 to SET2 was found to be different between the 2 groups ($P < .001$). We found no significant difference between the control and AF groups at SET1 (difference, 3.50 bpm; CI, -29.3 bpm, 36.3 bpm; $P = .96$). However, the AF horses had a higher HR_{max} at SET2 compared with the control group (difference, 87 bpm; CI, 54.2 bpm, 119.8 bpm; $P < .0001$).

3.3 | Velocity at HR of 200 bpm (V_{200})

For the control group, the V_{200} was 8.03 ± 0.07 and 7.92 ± 0.93 m/sec at SET1 and SET2, respectively. For the AF group, the V_{200} was 8.08 ± 0.53 and 5.21 ± 0.22 m/sec, respectively (Figure 1A,B).

A significant change in V_{200} between the 2 groups from SET1 to SET2 was found ($P = .002$). No significant difference was found between the control and AF groups at SET1 (difference, 0.00 m/sec;

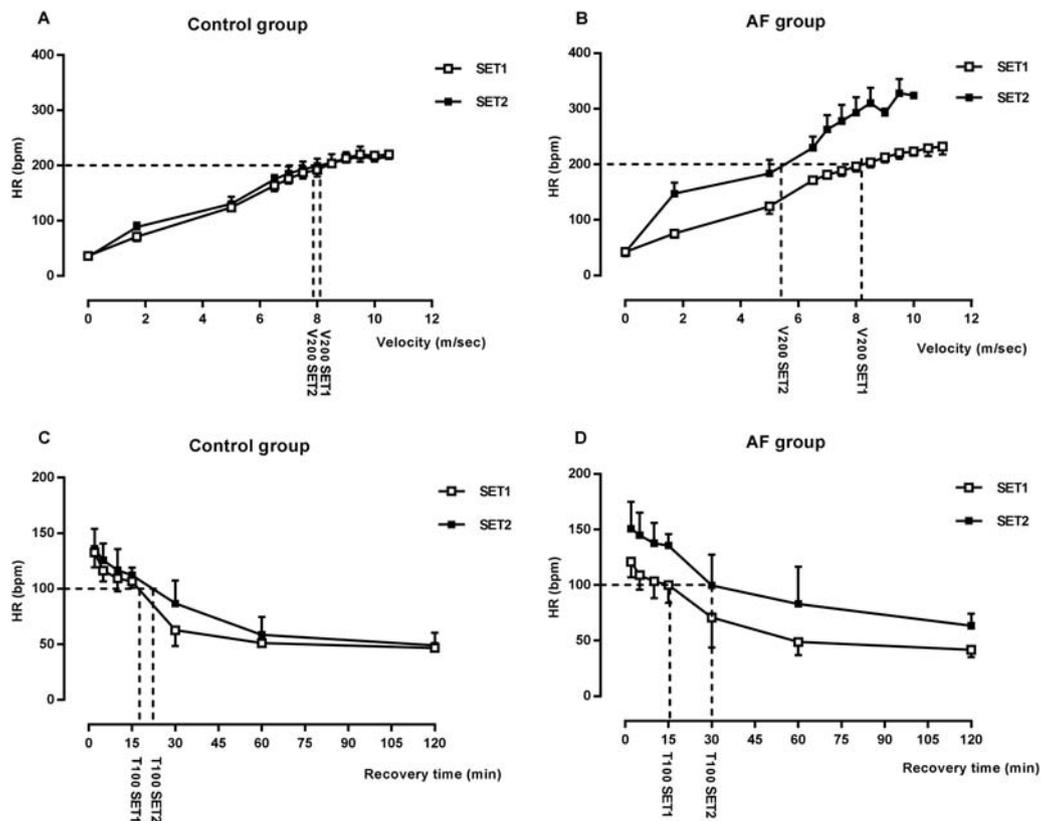


FIGURE 1 Heart rate during the exercise tests and in the recovery period. Mean \pm SD heart rate for SET1 and SET2 for the control and AF horses at different treadmill velocities (A and B). Heart rate during the recovery period of up to 120 minutes after cessation of exercise test is shown in C and D

TABLE 1 Prevalence of horses with abnormal QRS complexes during exercise and in the recovery period

	SET	Rhythm	Exercise			Post exercise (120 min)		
			Single abnormal QRS complexes	Couplets	WCT	Single abnormal QRS complexes	Couplets	WCT
Control horses	1	SR	0	0	0	1 (0–1)	0	0
	2	SR	1 (0–1)	0	0	0	0	0
AF horses	1	SR	1 (0–1)	0	0	2 (0–2)	2 (0–1)	0
	2	AF	6 (1–10)	5 (2–12)	3 (5–12)	1 (0–1)	0	0

Abbreviations: AF, atrial fibrillation; Couplets, two consecutive abnormal QRS complexes; WCT, wide complex tachycardia; SET, standardized exercise test; SR, sinus rhythm.

Number of horses developing abnormal QRS complexes during the exercise test (range specified in brackets).

CI, -0.56 m/sec, -0.56 m/sec; $P = 1.00$). However, at SET2, the AF horses had a lower V_{200} compared with the control group (difference, -2.45 m/sec; CI, -3.82 m/sec, -1.09 m/sec; $P < .0001$).

$P = .74$) and SET2 (difference, 21.69 minutes; CI, -13.42 minutes, 56.80 minutes; $P = .29$).

3.4 | Heart rate recovery

The HR_{mean} measured during the recovery period is shown in Figure 1C,D for the control and AF groups. For T_{100} , a significant difference was found between the 2 groups from SET1 to SET2 ($P = .046$). However, no changes were found when comparing the 2 groups at SET1 (difference, -4.33 minutes; CI, -19.08 minutes, 10.41 minutes;

3.5 | Abnormal QRS complexes

Only a few abnormal QRS complexes were observed for the control group and for SET1 of the AF group (when the horses were in SR). However, 5 of the 6 horses in SET2 of the AF group showed a high prevalence of abnormal QRS complexes, and 3 of the horses showed several episodes of wide complex tachycardia during the exercise tests (Table 1). Figure 2 gives an example of an exercise ECG from 1 of the

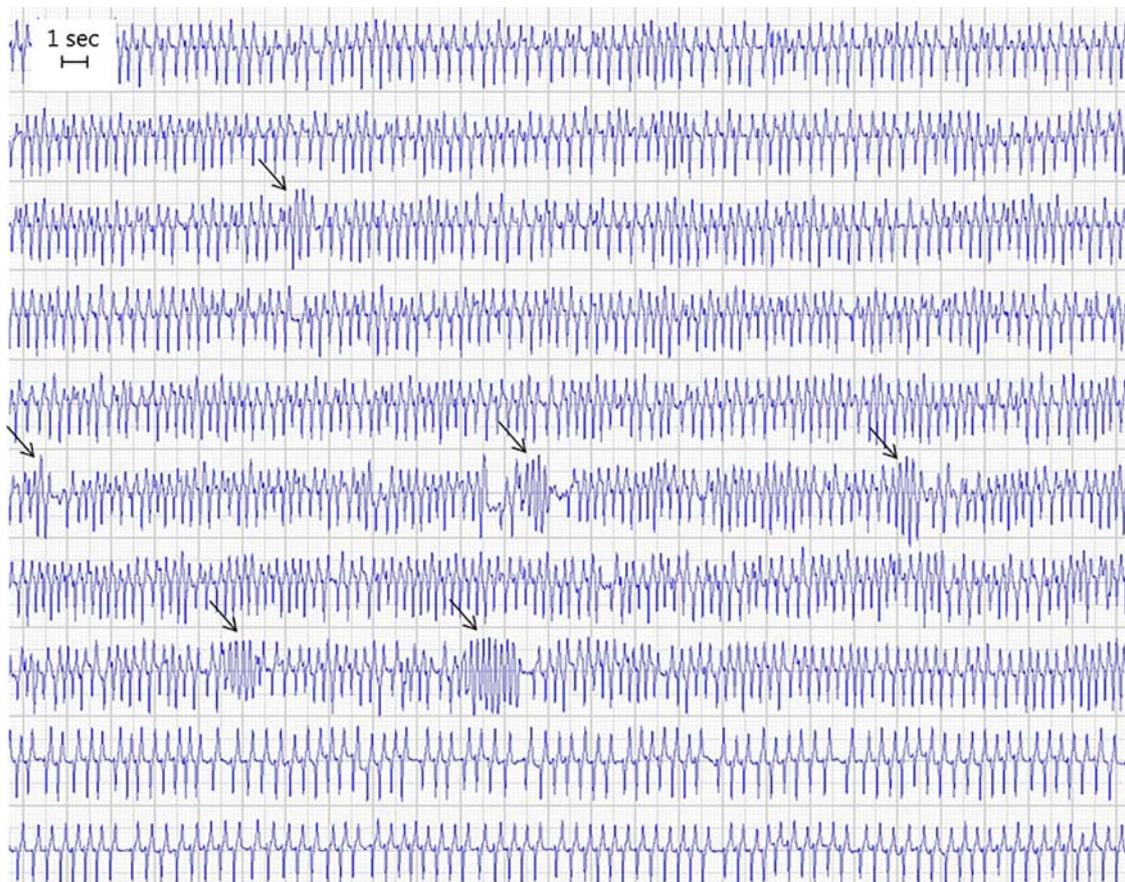


FIGURE 2 Overview of electrocardiogram (Lead II) from an exercise test. Six-minute continuous ECG (Lead II) from an exercise test (SET2) in a horse with AF. Arrows point to areas where abnormal QRS complexes are present

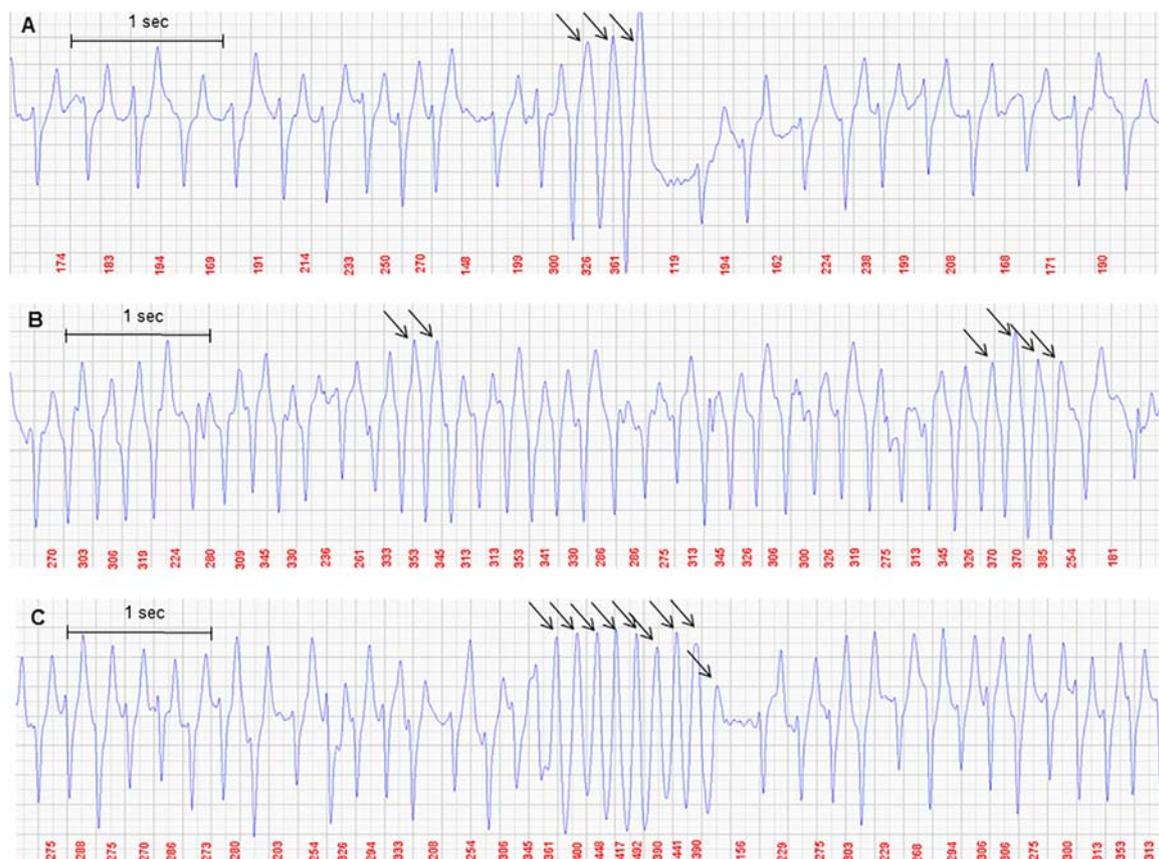


FIGURE 3 Electrocardiograms (Lead II) showing abnormal QRS complexes with R-on-T phenomenon. A is from a horse during the warm-up period for SET2; B and C are examples during maximum exercise. Arrows point to abnormal QRS complexes. The instantaneous heart rate is shown in red

AF horses (SET2). Examples of abnormal QRS complexes with the R-on-T phenomenon during exercise (including the instantaneous HR) are shown in Figure 3.

3.6 | Hematological variables

Results of K^+ , Na^+ , Cl^- , Ca^{2+} , lactate, glucose, PCV, PP, and pH for the time points described above for both the control and AF groups are shown in Figures S1 and S2 in the Supporting Information. During each exercise test, K^+ increased above the upper limit of the reference interval, whereas Ca^{2+} decreased and Na^+ and Cl^- increased only slightly. The blood glucose concentration increased above the reference interval in the post-exercise period, and PCV (and to a lesser extent PP) increased, whereas pH decreased during the exercise test. A significant change was found for Na^+ , Ca^{2+} , and PP between the control and AF groups from SET1 to SET2 ($P = .009$, $P = .027$, and $P = .031$, respectively), but no significant difference was found between the control and AF groups for SET1 or SET2.

Lactate increased for all groups during each SET, and the concentrations continued to increase for 2–5 minutes after cessation of the exercise test. For the control group, the V_{LA4} was 7.92 ± 0.61 m/sec at SET1 and all 3 results were in the interval 6.50–7.00 m/sec at SET2. For the AF group, the V_{LA4} was 8.25 ± 0.75 and 7.80 ± 0.48 m/sec at SET1 and SET2, respectively. We found no change in V_{LA4} between the 2 groups

from SET1 to SET2 ($P = .21$), and no significant difference was found between the control and AF groups at SET1 (difference, -0.33 m/sec; CI, -0.73 m/sec, 1.40 m/sec; $P = .73$). However, the AF horses had higher V_{LA4} at SET2 compared with the control group (difference, 0.83 m/sec; CI, 0.39 m/sec, 1.28 m/sec; $P < .0001$). The maximum lactate concentration for control horses was 17.6 ± 2.5 mmol/L for SET1 and 25.3 ± 8.1 mmol/L for SET2, and for the AF group, LA_{max} was 19.1 ± 6.9 and 18.1 ± 8.4 mmol/L for SET1 and SET2, respectively. No significant difference was found between the 2 groups at SET2 ($P = .25$). Within 2 hours of the exercise test, the lactate concentration was < 2 mmol/L for all but 1 horse, that had a lactate concentration of 2.3 mmol/L.

4 | DISCUSSION

To the best of our knowledge, our study is the first to quantify the effect of AF on performance in Standardbred trotters during a high-intensity exercise test. The results confirm that AF is detrimental to athletic performance, and characterized by decreased velocity, an increase in HR to an extent far above the normal accepted maximum HR and decreased V_{200} . In addition, we observed a high prevalence of abnormal QRS complexes during exercise.

It is well known that horses with AF have a limited capacity for exercise because of decreased cardiac output secondary to decreased

atrial contraction, tachycardia and irregular rhythm.^{2,3,16,24} However, our study has quantified the velocity reduction at approximately 12%, which is in agreement with a study in human AF patients, which reported a decrease in exercise capacity of 15% compared with patients in SR.²⁵

A linear correlation exists between HR during exercise and oxygen uptake in athletes in SR.²⁶ However, the relationship between HR and exercise capacity during AF is unclear because of the complex interaction between decreased atrial function, ventricular diastolic filling time and irregular HR.²⁷ The autonomic nervous system plays a pivotal role in regulating cardiac rhythm and rate. In horses with structurally normal hearts, at rest, the dominant parasympathetic tone will prevent the high number of atrial electrical impulses during AF from being transmitted to the ventricles via the atrioventricular (AV) node by increasing AV nodal refractoriness. As a result, a normal or slightly increased HR is present in most horses in AF.^{28,29} During this period, the bombardment of the AV node by AF impulses results in concealment of many of these impulses within the AV node, thereby ensuring a low ventricular rate.²⁹ During exercise or stress, sympathetic drive dominates, resulting in a shortening of the AV nodal refractory period, thereby allowing for increased ventricular stimulation, resulting in an increased ventricular rate.³⁰ Our study identified an extreme increase in HR in the horses during exercise. This finding is in agreement with a previous study, in which a HR of up to 492 bpm was recorded in horses in AF during a submaximal lunging test.¹⁷ A submaximal exercise test performed in warmblood horses in AF also showed an increased HR compared with healthy controls,¹⁶ but it was not as high as the other reported values¹⁷ and our findings.

Estimating HR during AF is challenging because of the high RR variation, typical for this arrhythmia. The RR variation in horses in SR during exercise has been estimated at <4%, making an instantaneous HR calculation based on a single RR interval a valid estimate of HR in horses with SR.²⁰ To overcome the large RR variation during AF, we calculated HR_{mean} as a mean of 25 beats, which consequently yielded a lower HR than if the single shortest RR interval had been measured. The HR response to exercise in human patients with AF varies among studies. One study found no significant difference in HR at submaximal and peak exercise levels between AF and control subjects,²⁵ whereas other studies report increases in HR during exercise in human patients with AF as compared with patients with SR.^{27,31–34} In human patients with chronic AF, the primary goal of rate-control treatment is to control the rapid HR response at rest and during exercise, often by beta-adrenergic blockade, which decreases HR and blood pressure.^{27,33} In 1 study, the rate control resulted in decreased exercise capacity because of decreased oxygen uptake,³¹ whereas another study combining several HR-reducing medications showed an improvement in exercise tolerance.³⁵ High HR may be interpreted as a compensatory mechanism for the body to maintain sufficient cardiac output during exercise because of a lack of atrial contraction caused by AF. However, the results of our study, showing decreased V_{max} and increased V_{LA4} for the horses in AF, indicate that the tachycardia does not appear to compensate fully for compromised exercise capacity and is not sufficient to ensure adequate oxygenation of the body.³⁴ Therefore, there is no

clear conclusion about whether or not high HR is a beneficial adaptive response to increased physical demands.

The irregular electrical conduction from atria to ventricles as well as the exceedingly fast ventricular response rate during AF have profound effects on ventricular electrophysiology. Three of the 6 horses showed a high number of wide complex tachycardias with R-on-T morphology during exercise, and this high prevalence is in agreement with a previous study.¹⁷ In normal Standardbred trotters, the prevalence of single abnormal QRS complexes during racing has been reported at between 0% and 4%, whereas the prevalence in the immediate period after racing is approximately 20%.^{36,37} These findings are in agreement with the results of the exercise tests performed in our study on horses during SR. The literature includes only limited descriptions of the development of ventricular arrhythmias during exercise in human AF patients, but some AF patients have exercise-induced ventricular tachycardia, and rate-controlling drugs such as procainamide, propafenone, and sotalol may decrease the prevalence of premature ventricular beats.³⁸ Whether this approach could be used in horses during exercise to decrease ventricular arrhythmias needs to be studied further.

Defining and detecting the origin of ventricular arrhythmias based on a 2-lead surface ECG (as used here) is challenging. Supraventricular beats can have a wide (prolonged, aberrant) QRS morphology at normal HR, if caused by bundle branch block, or intermittently, if associated with premature supraventricular beats. In the latter case, widening of the QRS is caused by partial refractoriness of the ventricular conduction tissue because of the prematurity of the beat. This type of aberrancy may be considered benign, because it disappears when the HR decreased. Presence of P waves preceding wide-QRS morphology complexes may aid in diagnosing it as supraventricular in origin, as opposed to ventricular premature beats.³⁹ In ventricular ectopy, the QRS morphology is abnormal (wide) because of the ventricular origin of the beats with slow intraventricular conduction. Ventricular ectopy can be a serious arrhythmia, which, depending on the rate, can cause collapse or even sudden death because of ventricular tachycardia or ventricular fibrillation, respectively.

Because of the high HR during exercise, presence of P waves often cannot be ascertained, thus differentiating wide QRS complex tachycardias as ventricular versus supraventricular in origin may be difficult or impossible. We were not able to differentiate the 2 conduction patterns in our study, because doing so would require intracardiac His bundle electrocardiography recordings.⁴⁰ The treadmill test is considered a stressful experience for horses, leading to high sympathetic stimulation, which may explain the HR increase initiated during the warm-up period, permitting a high number of atrial impulses to be transmitted through the AV node. The stressful situation may allow for the aberrant conduction process to predominate. However, higher sympathetic tone also would enhance automaticity and possibly allow for more ectopic beats to occur. Consequently, a definite conclusion on the origin of the abnormal beats in our study cannot be made.

Hematologic and biochemical variables followed a consistent and repeatable pattern of changes during and after the exercise tests, and the results generally are in agreement with previous studies conducted

in healthy Thoroughbreds performing a maximum exercise test on a treadmill.^{41,42} Although no significant changes could be detected between SET1 and SET2, lactate seemed to increase for the control horses in SET2 compared to SET1 (Figure S2A in the Supporting Information), which most likely can be explained by the increased velocity experienced in 2 of the control horses during SET2, when these 2 horses managed to run for 2 minutes longer than in SET1. Maximum lactate concentration (LA_{max}) and V_{LA4} may not be valid markers of exercise tolerance in AF horses; because it is likely, they will run for a shorter duration with subsequently decreased lactate production. This was, however, not confirmed by our results. After exercise, the horses were walked for 30 minutes and lactate clearance from the blood was almost completed after 2 hours. This finding is in consistent with a previous study in racehorses showing fast lactate removal in horses that are walked after maximal exercise.⁴³ Plasma protein concentration was lower in the AF group at rest and during and after SET2, compared with SET1 (Figure S2H in the Supporting Information). In our analysis of PP at SET2, we observed a significantly lower result in AF horses, a finding that has not been reported previously in horses. Lower plasma albumin concentration has been reported in human patients with paroxysmal AF,⁴⁴ whereas another study found the protein serum amyloid A was increased in AF patients.⁴⁵ Because individual proteins were not measured in our study, we cannot differentiate the source of the protein changes.

A significant effect of observer on treadmill velocity was found, because 1 observer allowed horses to run faster before fatigue was determined compared with the other observer. This finding highlights the subjective definition of fatigue and effect of observer therefore is relevant to include in the statistical analyses.

All horses gained weight during the study period, which may have had a detrimental effect on the performance capacity at the second exercise test. Detraining during the study period also may result in poorer performance. To minimize the effect of detraining, all horses recruited had been out of training for at least 2 months before initiation of the trial. Because 2 of our control horses were able to run faster in the second exercise test compared with the first, we assume that neither detraining nor weight gain can explain the decreased velocity observed in the AF horses during their second exercise test. Despite the horses being untrained, the exercise tolerance parameters V_{200} and V_{LA4} calculated in SR at SET1 were comparable to those of racing Standardbred mares.⁴⁶

Although it is uncommon, collapse during exercise has been reported in horses with AF.⁴⁷ The high HR and abnormal QRS complexes observed here and supported by results from another study¹⁷ lead us to question whether AF horses should be considered safe for riding purposes. A recently published consensus statement recommends retiring AF horses when their HR exceeds 220 bpm during sustained maximum exercise, or if ventricular arrhythmias are detected during exercise.²¹ The recommendations for horses are in agreement with guidelines for humans, allowing athletes with AF a certain amount of exercise under strict HR control and in the absence of hemodynamic impairment, and with the recommendation to stop activity when they experience palpitations.⁴⁸ Based on these recommendations, all 6

horses in our study should be considered unsafe for riding purposes. Future prospective studies looking into the risk of sudden cardiac death and collapse in horses with spontaneous AF are needed to determine whether these recommendations are too strict. Additionally, acquiring intracardiac recordings while AF horses are exercising would help investigate the origin of the abnormal QRS complexes encountered. Our findings evidently support the use of exercise ECGs when assessing performance horses with AF.

No race-fit horses were included, and this may be seen as a limitation of our study. In addition, only horses with induced AF were included and therefore no horses with spontaneous AF were studied. We were unable to determine whether the induction of AF resulted in myocardial damage unrelated to AF itself and future studies could address this issue by performing an additional SET after cardioverting the AF group back to SR. The sham-operated control group may be underpowered because of the low number of horses, which may have resulted in a type II error. Ideally, more horses would have been included.

In conclusion, horses with induced AF showed decreased performance during a SET to fatigue, as measured by decreased V_{max} and V_{200} . Additionally, a marked increase in HR was observed during exercise, with HR_{max} between 276 and 346 bpm. Five of 6 horses in AF showed a high prevalence of abnormal QRS complexes when exercising, and several episodes of wide complex tachycardia with R-on-T phenomenon were observed in 3 of the horses. We could not determine whether the abnormal beats were of ventricular origin or if they should have been characterized as aberrant beats originating from the atria. No horses collapsed during the tests, but based on the present and previous studies,^{16,17} horses with AF should undergo exercise testing to determine whether or not they should be used for riding purposes.

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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 study was approved by the local ethical committee at the Department of Veterinary Clinical Sciences, University of Copenhagen and The Danish Animal Experiments Inspectorate (license number 2015-15-0201-00693) and was performed in accordance with the European Commission Directive 86/609/EEC.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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