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# Effect of sotalol on heart rate, QT interval, and atrial fibrillation cycle length in horses with atrial fibrillation

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12A4214N (to A. Decloedt), 1134917N (to  
L. Vera), 1S56217N (G. Van Steenkiste)**Background:** Based on its pharmacokinetic profile and electrophysiological effects in healthy horses, sotalol potentially could be used as a long-term PO antiarrhythmic drug in horses.**Objectives:** To evaluate the effect of sotalol on heart rate (HR), QT interval, atrial fibrillatory rate, and success of cardioversion in horses with naturally occurring chronic atrial fibrillation (AF).**Animals:** Twenty-eight horses referred for transvenous electrical cardioversion of AF were treated with 2 mg/kg sotalol PO q12h for 3 days before cardioversion, and 13 horses underwent the same protocol without sotalol administration.**Methods:** Retrospective study. Before and after sotalol or no treatment, the HR was measured at rest and during an exercise test. The QT interval and atrial fibrillation cycle length (AFCL) were measured at rest using tissue Doppler velocity imaging.**Results:** In the control group, no significant differences were found between the 2 examinations. In the sotalol group, the HR at rest and during exercise was significantly lower after sotalol treatment, whereas the QT interval and AFCL measured by tissue Doppler increased significantly. Cardioversion to sinus rhythm was achieved in 25/28 horses in the sotalol group and all horses in the control group, but the median number of shocks and energy at cardioversion were significantly lower in the sotalol group.**Conclusions and Clinical Importance:** In horses with AF, sotalol administration results in class III antiarrhythmic effects and  $\beta$ -blocking activity, with moderate HR reduction during exercise.**KEYWORDS**

antiarrhythmic therapy, arrhythmia, echocardiography, electrocardiography, equine

**Abbreviations:** AERP, atrial effective refractory period; AF, atrial fibrillation; AFCL, atrial fibrillation cycle length; ERP, effective refractory period; HR, heart rate; TVEC, transvenous electrical cardioversion.

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This study was carried out at the Department of Large Animal Internal  
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## 1 | INTRODUCTION

Atrial fibrillation (AF) is a relatively common arrhythmia in horses, which often presents as so-called "lone AF" without underlying structural cardiac disease. Pharmacological or transvenous electrical cardioversion (TVEC) to sinus rhythm is usually recommended in equine

athletes because AF limits performance in horses used for intensive athletic work. Even at lower levels of exercise intensity, horses in AF might exhibit extremely high heart rates (HRs), and collapse has been described.<sup>1</sup> The success rate for both pharmacological cardioversion and TVEC is very high, but AF recurrence after treatment is common with an overall rate of recurrence up to 39% at 1 year after cardioversion.<sup>2–5</sup> The pathophysiology of AF initiation and perpetuation in horses has not yet been completely elucidated. Factors that might be associated with AF recurrence include structural changes to the atrial myocardium, atrial size and stretch, short atrial effective refractory period (AERP), and supraventricular ectopic foci.<sup>2,6</sup> Long-term antiarrhythmic treatment could be used to prevent AF recurrence after cardioversion through different mechanisms such as increasing AERP, decreasing supraventricular ectopy, and decreasing vulnerability to AF initiation. As has been shown in humans, dogs, and horses, sotalol and other class III antiarrhythmic drugs lead to lengthening of the repolarization phase of the action potential by blocking the outward rapid delayed rectifier potassium current. This leads to an increase in refractoriness of the tissues. Aside from reversing the shortening of the monophasic action potential and effective refractory period (ERP) caused by atrial remodeling during AF, lengthening of the ERP also decreases the excitability of the cardiac tissues. Therefore, a decrease in ectopic discharges and a decrease in substrate for re-entry are likely. In addition, antiarrhythmic treatment might be useful to decrease the HR at rest or during exertion in horses in AF. This rate control therapy possibly could decrease the risk of collapse and sudden cardiac death. However, long-term PO antiarrhythmic therapy is rare in horses, and the drugs also might have proarrhythmic effects.

Sotalol can be safely administered with intermediate PO bioavailability in horses.<sup>7</sup> In human medicine, sotalol is not commonly used for cardioversion of AF, but it is frequently used as an effective drug for prevention of AF recurrence after cardioversion.<sup>8,9</sup> Electrophysiological effects of sotalol include increased QT interval, decreased HR, and prolongation of the atrioventricular nodal refractory period and PQ interval. In veterinary medicine, sotalol is the most commonly used long-term treatment for hemodynamically important ventricular arrhythmias in dogs and cats.<sup>10</sup> In healthy horses, sotalol results in prolongation of the QT interval.<sup>7,11</sup> However, the use of sotalol has not been described in horses with cardiac arrhythmias, except in 2 recent reports describing single cases.<sup>12,13</sup>

Our objectives were to assess the effect of sotalol on HR, QT interval, atrial fibrillatory rate, and success of cardioversion in horses with AF. We hypothesized that sotalol administration would result in a decreased HR at rest and during exercise, a prolonged QT interval and a decreased atrial fibrillatory rate.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design

The study population consisted of 41 horses consecutively admitted for TVEC treatment of AF at the Department of Large Animal Internal Medicine at the Faculty of Veterinary Medicine, Ghent University. All horses were examined by an ECG at rest of at least 2 hours duration, an ECG during a lunging exercise test<sup>14</sup> and echocardiography. After the initial

measurements at admission, the first 28 horses were treated PO with 2 mg/kg sotalol (Sotalol Sandoz, Sandoz, Vilvoorde, Belgium) q12h for 3 days before cardioversion. Echocardiography was repeated just before TVEC, after 6 doses of sotalol had been administered. The ECG at rest was repeated after at least 5 doses of sotalol, and the exercise test after at least 4 doses of sotalol. Data always were collected approximately 2–3 hours after sotalol administration. To determine measurement repeatability, 13 horses underwent the same protocol without sotalol administration. The TVEC was performed according to procedures described previously.<sup>4,15</sup> Shocks were administered under general anesthesia using stepwise increases of the delivered energy (150, 200, 250, 300, and 360 J) until cardioversion. If cardioversion did not occur after the 360 J shock, the catheters were repositioned and more high energy shocks were administered.

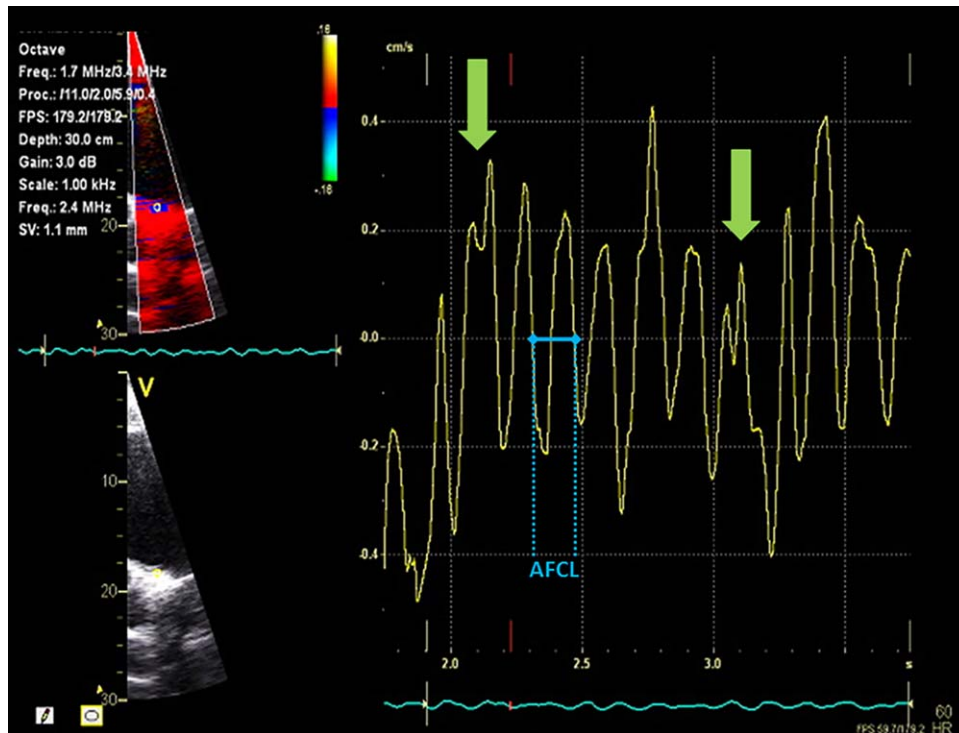
### 2.2 | Measurements

The HR at rest was measured from the resting ECG (Televet 100, Engel Engineering Services GmbH, Heusenstamm, Germany) as an average over a 30-minute period. The QT interval was measured at rest using the Televet software calipers (Televet 100, Engel Engineering Services GmbH), as an average from 10 RR intervals with an instantaneous HR of the preceding RR interval of 35–45 bpm.<sup>16</sup> The lunging exercise test consisted of 5 minutes of walk, 10 minutes of trot, 4 minutes of canter, and 1 minute of gallop. The test was terminated early if the horse showed an excessively high HR or frequent QRS complexes with an R-on-T morphology. The HR at walk, trot, and canter was measured over 2 minutes, starting at least 1 minute after the gait transition in order to obtain a relatively stable HR. The HR during gallop was measured over the entire gallop phase.

The atrial fibrillatory rate was assessed from tissue Doppler velocity curves of the atrial myocardial walls, as described previously.<sup>17,18</sup> In brief, tissue Doppler images were acquired from the left atrial free wall in a right parasternal 4-chamber view, from the right atrial dorsal wall at the level of the tuberculum intervenosum in a right parasternal view and from the left atrial free wall in a left parasternal long axis view. The probe frequency was 1.7/3.4 MHz, the image width was 30°, image depth ranged from 22 to 30 cm, and the velocity scale was +16/–16 cm/s (Vivid 7, GE Healthcare, Diegem, Belgium). This resulted in a frame rate of > 180 frames per second. From each view, 10 loops with a long RR interval ( $\geq 2$  s) were stored. Tissue Doppler velocity curves were acquired off-line by positioning a  $5 \times 5$  mm sample volume in the atrial myocardial wall (Echopac software version 11.2, GE Healthcare, Diegem, Belgium). The atrial fibrillation cycle length (AFCL) was measured from consecutive loops with at least moderate quality, until a minimum of 30 AFCL were measured from each view (Figure 1).<sup>17,18</sup> These 30 measurements then were averaged to obtain AFCL from each view. Data were measured by the same experienced observer (B. Broux for ECG and A. Decloedt for echocardiographic measurements) with the observer blinded to the identity of the horse and treatment status.

### 2.3 | Statistics

The number of horses that received sotalol was determined using power calculation software (G\*Power 3.1.9.2, Franz Faul, Universität



**FIGURE 1** Tissue Doppler velocity curve of the left atrial free wall from a left parasternal long axis view with moderate quality (the lowest quality still included in the study). The biphasic atrial velocity pattern can be distinguished but there is presence of artifacts, indicated by green arrows. The blue line demonstrates 1 atrial fibrillation cycle length (AFCL) measurement

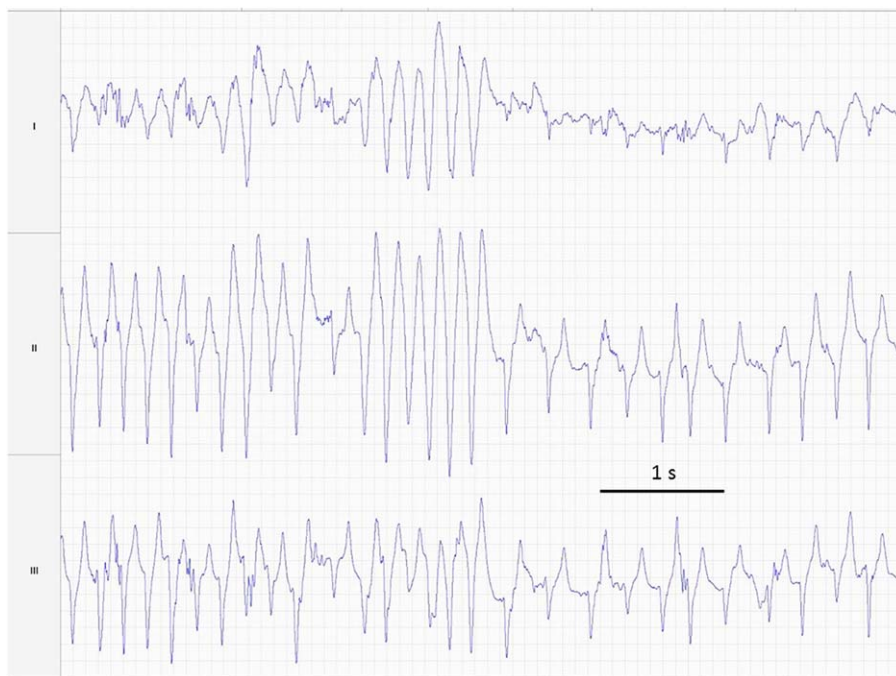
Kiel, Germany) based on a paired comparison with a hypothesized increase of AFCL of 5 ms and a standard deviation (SD) within the population of 20 ms. Based on this calculation, a sample size of 28 horses could detect a significant difference with a 2-sided  $\alpha$  of 5% and  $\beta$  of 20%. Data were analyzed using dedicated software (SPSS Statistics version 24, IBM, Armonk, New York). Normality of the data was checked using visual inspection, the Kolmogorov-Smirnov test, and Shapiro-Wilk test. HR, QT interval, and AFCL were compared between groups (sotalol administration or no treatment) and timing (before or after treatment) using a mixed model with horse as the unit of repeated measure and treatment and timing as fixed effects. Post hoc Bonferroni correction was applied for multiple pairwise comparisons. Height, body weight, age, duration of AF, and cardioversion data were compared between the sotalol group and the control group using an independent *t* test for normally distributed variables or the Mann-Whitney test for non-normally distributed data. The level of significance was defined as  $P < .05$ .

### 3 | RESULTS

The sotalol group consisted of 23 Warmbloods, 3 trotters, 1 Paint, and 1 Appaloosa, with a height of  $169 \pm 7$  cm (mean, SD), weighing  $565 \pm 65$  kg, and aged  $9 \pm 3$  years. The control group consisted of 12 Warmbloods and 1 trotter, with a height of  $172 \pm 6$  cm, weighing  $605 \pm 60$  kg, and aged  $10 \pm 3$  years. Height, body weight, age, and duration of AF were not significantly different between groups ( $P \geq .05$ ). No adverse effects of sotalol administration were noticed, except for

transient local sweating. During exercise, 4/13 (31%) horses in the group without treatment showed QRS complexes with an R-on-T morphology during the first test compared to 3/13 horses (23%) during the second test. In the sotalol group, 5/21 (24%) horses showed QRS complexes with an R-on-T morphology both before and after treatment (Figure 2). The R-on-T morphology was not consistently present in the same horses during both exercise tests. In total, 7 horses in the sotalol group and 5 horses in the control group showed R-on-T morphology during either the first or the second test. Cardioversion to sinus rhythm was achieved by the TVEC procedure in 25/28 horses in the sotalol group and in all horses in the control group. One of the horses that did not convert underwent a successful second TVEC procedure with amiodarone premedication 2 weeks later. Two horses in the sotalol group showed early recurrence of AF. In 1 horse, recurrence occurred during anesthesia and the horse was converted to stable sinus rhythm during the same procedure. In the second horse, recurrence occurred during recovery. The horse was reanesthetized on the same day and converted to stable sinus rhythm. Amiodarone was administered IV (5 mg/kg over 30 minutes) to both horses during and immediately after the second cardioversion. The median number of shocks required for cardioversion to sinus rhythm was 1 (range, 1–4) in the sotalol group, compared to 3 (range, 1–8) in the control group ( $P = .016$ ). The median energy of the shock at cardioversion was 150 J (range, 150–300 J) in the sotalol group, and 250 J (range, 150–360 J) in the control group ( $P = .023$ ).

The resting HR, QT interval, HRs during exercise, and AFCL before and after treatment are summarized in Table 1 for the sotalol group



**FIGURE 2** High heart rate and QRS complexes with an R-on-T morphology in 1 horse in the sotalol group, after which the exercise test was terminated early

and the control group. Within the sotalol group, the resting HR and the HRs during exercise decreased after treatment compared to before treatment (Figure 3A), whereas the QT interval and the AFCL measured in the right atrium and the left atrial free wall from the left parasternal view increased. In the control group, no significant differences were found between the 2 examinations (Figure 3B). Compared to the control group, horses in the sotalol group had lower resting HR, lower HR during trot and increased QT interval.

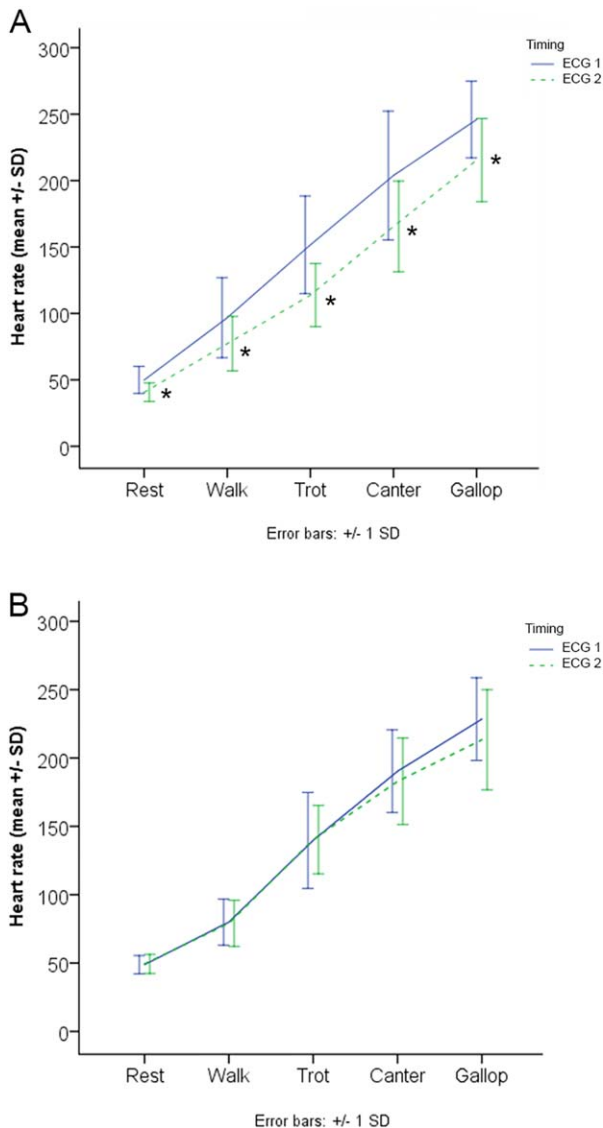
#### 4 | DISCUSSION

We describe the effects of sotalol administered PO to horses with AF. Sotalol treatment resulted in a decrease in HR at rest and during exercise, a prolongation of the QT interval and an increase in AFCL. Significantly less energy was required for electrical cardioversion in the sotalol group, although cardioversion could not be achieved in 3/28 horses, of which 1 horse converted during a second TVEC procedure.

**TABLE 1** Resting HR, QT interval, heart rates during exercise, and AFCL before and after treatment for the sotalol group (n = 28) and the control group (n = 13)

|                          | Sotalol group    |          |                  |          |    |                          | Control group      |          |                    |          |    |                          |
|--------------------------|------------------|----------|------------------|----------|----|--------------------------|--------------------|----------|--------------------|----------|----|--------------------------|
|                          | Mean             | ECG 1 SD | Mean             | ECG 2 SD | N  | Difference Mean (95% CI) | Mean               | ECG 1 SD | Mean               | ECG 2 SD | N  | Difference Mean (95% CI) |
| HR rest (bpm)            | 50 <sup>a</sup>  | 10       | 41 <sup>b</sup>  | 6        | 28 | 9 (5 to 15)              | 49 <sup>a</sup>    | 7        | 49 <sup>a,b</sup>  | 7        | 13 | 1 (-4 to +3)             |
| QT rest (ms)             | 513 <sup>a</sup> | 41       | 560 <sup>b</sup> | 52       | 28 | -47 (32 to 62)           | 521 <sup>a</sup>   | 23       | 521 <sup>a,b</sup> | 40       | 13 | 0 (-18 to +18)           |
| HR walk (bpm)            | 97 <sup>a</sup>  | 30       | 77 <sup>b</sup>  | 20       | 21 | 20 (9 to 30)             | 80 <sup>a,b</sup>  | 17       | 79 <sup>a,b</sup>  | 17       | 13 | 1 (-13 to +15)           |
| HR trot (bpm)            | 152 <sup>a</sup> | 37       | 114 <sup>b</sup> | 24       | 21 | 38 (23 to 52)            | 140 <sup>a,b</sup> | 35       | 140 <sup>a</sup>   | 25       | 13 | 1 (-10 to +9)            |
| HR canter (bpm)          | 204 <sup>a</sup> | 48       | 165 <sup>b</sup> | 34       | 21 | 38 (23 to 54)            | 190 <sup>a,b</sup> | 30       | 183 <sup>a,b</sup> | 32       | 12 | 7 (-1 to +16)            |
| HR gallop (bpm)          | 246 <sup>a</sup> | 29       | 215 <sup>b</sup> | 31       | 18 | 32 (14 to 50)            | 228 <sup>a,b</sup> | 30       | 213 <sup>b</sup>   | 37       | 11 | 18 (1 to +35)            |
| AFCL <sub>4CH</sub> (ms) | 138              | 13       | 144              | 16       | 28 | -6 (-11 to 0)            | 145                | 12       | 138                | 18       | 11 | 7 (0 to +13)             |
| AFCL <sub>RA</sub> (ms)  | 171 <sup>a</sup> | 16       | 181 <sup>b</sup> | 13       | 28 | -10 (-15 to -5)          | 179 <sup>a,b</sup> | 13       | 180 <sup>a,b</sup> | 16       | 13 | -1 (-9 to +7)            |
| AFCL <sub>LLA</sub> (ms) | 151 <sup>a</sup> | 13       | 161 <sup>b</sup> | 16       | 28 | -10 (-15 to -5)          | 158 <sup>a,b</sup> | 11       | 160 <sup>a,b</sup> | 13       | 13 | -2 (-7 to +4)            |

Abbreviations: HR rest, heart rate at rest; bpm, beats per minute; QT rest, QT interval at rest; HR walk, heart rate during walk; HR trot, heart rate during trot; HR canter, heart rate during canter; HR gallop, heart rate during gallop; AFCL<sub>4CH</sub>, atrial fibrillation cycle length measured in the left atrial free wall from the 4 chamber view; AFCL<sub>RA</sub>, atrial fibrillation cycle length from the right atrial dorsal wall at the level of the tuberculum intervenosum in a right parasternal view; AFCL<sub>LLA</sub>, atrial fibrillation cycle length measured in the left atrial free wall from the left parasternal long-axis view. Significant differences between groups are indicated by different superscripts (P < .05).



**FIGURE 3** Heart rate at rest and during the exercise test (mean, SD) in the sotalol group (A) and the control group (B). Significant differences between the 2 examinations (before and after treatment for the sotalol group) have been indicated by an asterisk ( $P < .05$ )

The increased AFCL after sotalol treatment indicates slowing of the atrial activation rate. During AF, the AFCL is somewhat longer than the AERP because of the presence of a small excitable gap.<sup>19</sup> The prolongation of AFCL after sotalol administration can be attributed to an increase in the AERP or to widening of the temporal excitable gap. A previous study in goats described a 24% increase of the AFCL during IV sotalol infusion at 0.2 mg/kg/min.<sup>20</sup> This mainly resulted from widening of the temporal excitable gap, while the AERP remained stable. Sotalol administration in our study resulted in a modest increase of AFCL by approximately 6%. In comparison, IV administration of the class III antiarrhythmic drug amiodarone caused an AFCL increase up to 100% in horses with naturally occurring chronic AF.<sup>21</sup> In another study, the class I drug flecainide administered IV to horses resulted in an AFCL increase of approximately 35–50%.<sup>22,23</sup> This is in line with the

experimental study in goats, where administration of flecainide caused an AFCL increase of 48%.<sup>20</sup> This was attributed to widening of the temporal excitable gap, which results in decreased fragmentation of wavelets and fusion of waves. This causes a reduction of the number of wavelets in the atria and thus an increased chance of cardioversion.<sup>22</sup> Compared to amiodarone or flecainide, the effect of 2 mg/kg sotalol PO q12h on AFCL was limited, and cardioversion of AF using sotalol therapy alone seems unlikely in horses.

The limited effects of sotalol on AFCL can be explained by several factors. First, the sotalol plasma concentrations were probably below the therapeutic range described in human medicine. Plasma concentrations were not measured in our study, but the steady state plasma concentration was 287 ng/mL in horses receiving 2 mg/kg body weight sotalol PO twice daily for 9 days, while fed hay ad libitum during the day.<sup>11</sup> This is lower than the therapeutic plasma concentrations of 1000–3000 ng/mL described in human medicine.<sup>24</sup> However, the significant QT prolongation indicates class III activity despite the low plasma concentrations. The limited effects on the AFCL also can be explained by the reverse use dependence of the effect of sotalol on atrial refractoriness, implying decreased class III effects at more rapid atrial rates.<sup>25</sup> Reverse use dependence of sotalol probably limits the efficacy of sotalol against naturally occurring chronic AF with short AFCL, compared to use-dependent drugs such as propafenone. Finally, the effect of sotalol also might be affected by electrical remodeling of the atrial myocardium. Decreased electrophysiological actions of class III antiarrhythmic agents have been described in a goat model of chronic AF, and was explained by decreased contribution of the rapid delayed rectifier potassium current (IKr) to atrial repolarization in remodeled myocardium.<sup>26</sup>

The AFCL measured in the left atrial free wall from the right parasternal 4-chamber view was shorter compared to the other views, as has been described previously.<sup>17,18</sup> The AFCL from this view did not show a significant increase after sotalol administration. In the 4 chamber view, the atrial myocardium is located at a large image depth and more artifacts are present. This may explain the aberrant results from this view. Another possible explanation is spatiotemporal organization of AF, with high-frequency periodic sources, localized in the left atrium or the pulmonary veins that maintain AF. This has been described in a sheep model of induced AF.<sup>27</sup> Based on this hypothesis, sotalol might have little effect on AF sources in the left atrium, while it prolongs AFCL in the RA by widening of the temporal excitable gap. The left atrial wall visualized in the left parasternal view is closer to the interatrial septum than the left atrial free wall from the 4-chamber view, which may explain why the AFCL values were similar to those in the RA.

Sotalol administration resulted in a significantly lower HR at rest and during exercise. A 13–25% reduction in HR occurred after treatment. Atrial fibrillatory rate decreased by 6%, but this was unlikely to have contributed to a decrease in HR. Rather, the decreased HR likely was caused by the nonselective  $\beta$ -blocking activity of sotalol. As a competitive  $\beta$ -blocking agent, sotalol administration results in lower intracellular  $Ca^{2+}$  concentrations in the myocardial cells, causing a negative chronotropic effect by decreasing atrioventricular conduction.<sup>28</sup>

Sotalol could be a possible candidate drug for rate control therapy in horses with AF in which cardioversion is not possible or declined by the owner. Horses with AF often show no performance limitations during low-level exercise but are deemed at increased risk to ride if the average maximal HR during exercise, at an intensity that is at or slightly exceeding the horse's normal activities, exceeds 220/min, because high HR during exercise has been associated with collapse.<sup>1</sup> Long-term rate control therapy possibly could decrease the HR during exercise in these horses. Based on our study, it is unclear whether sotalol therapy could permanently decrease the exercising HR in horses with AF and whether riding a horse on sotalol is safe. First, the presence of QRS complexes with an R-on-T morphology was not decreased after sotalol treatment, and this might be associated with increased risk of ventricular fibrillation.<sup>14</sup> Second, sotalol is not recommended for rate control therapy in human medicine because of the risk of torsades de pointes and sudden cardiac death associated with QT prolongation.<sup>29</sup> The QT prolongation in our study was limited to 9%, whereas in human medicine an increase of 15%-20% is considered dangerous. Excessive QT prolongation might occur in horses when sotalol therapy is combined with other drugs, as has been described with general anesthesia.<sup>30</sup> Third, the  $\beta$ -blocking activity of sotalol might result in a negative inotropic effect and might affect blood pressure during exercise. However, the negative inotropic effect is counteracted by the class III activity, and no alterations of blood pressure have been described at rest in horses receiving sotalol.<sup>11</sup> Finally, sotalol cannot be used in horses during competition, because it is listed in the Fédération Equestre Internationale prohibited substances database as a controlled medication.

In human medicine, sotalol is used to maintain sinus rhythm after cardioversion of AF, although proarrhythmic effects and a small increase in all-cause mortality have been associated with its use.<sup>31</sup> Our study did not evaluate whether sotalol decreases the risk of AF recurrence, because doing so would require a long-term follow-up study in which horses are randomly treated with sotalol or placebo after cardioversion.<sup>32</sup>

The main limitation of our study is that sotalol was not administered in a double-blinded fashion with random assignment of horses to either the treatment group or the control group. Instead, all horses admitted for AF treatment in the timespan of 1 year were administered sotalol before TVEC as part of the standard treatment protocol. The control group consisted of horses consecutively admitted for AF treatment in a different calendar year, during which sotalol administration was not part of the treatment protocol because of safety concerns when combined with general anesthesia or administration of amiodarone in case of early recurrence of AF. The same study protocol was followed. Therefore, no difference between the 2 groups was expected.

In conclusion, sotalol administration results in class III antiarrhythmic effects and  $\beta$ -blocking activity in horses with AF. Therefore, sotalol shows potential as a rate control drug in exercising horses with AF. However, the safety of sotalol administration needs further evaluation because the HR reduction after sotalol therapy was limited, the risk of R-on-T phenomenon was not decreased and the proarrhythmic effects during exercise are not known.

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## CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

## OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

## INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

## AUTHOR CONTRIBUTIONS

*Study design:* Decloedt, Broux, van Loon

*Study execution:* Decloedt, Broux, van Loon, De Clercq, Deprez, Vera, Ven, Van Steenkiste

*Data analysis and interpretation:* Decloedt, Broux, van Loon

*Preparation of the manuscript:* Decloedt, Broux, van Loon, De Clercq, Deprez, Vera, Ven, Van Steenkiste

*Final approval of the manuscript:* Decloedt, Broux, van Loon, De Clercq, Deprez, Vera, Ven, Van Steenkiste

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