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Long-term follow-up of atrial function after cardioversion of atrial fibrillation in horses

Annelies Decloedt *, Tinne Verheyen, Nicky Van Der Vekens, Stanislas Sys, Dominique De Clercq, Gunther van Loon

Department of Large Animal Internal Medicine, Faculty of Veterinary Medicine, Ghent University, Salisburylaan 133, 9820 Merelbeke, Belgium

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ABSTRACT

Atrial fibrillation (AF) causes atrial electrical and contractile remodelling in horses. The aim of this study was to quantify left atrial (LA) contractile function and its time course of recovery after cardioversion of naturally-occurring AF in horses. The study population included 42 AF horses which were successfully treated using transvenous electrical cardioversion TVEC ($n = 39$) or quinidine sulfate ($n = 3$), with trivial or mild mitral regurgitation present in 25 horses. Thirty-seven healthy horses were used as controls. AF duration was estimated based on the history and previous examinations. Echocardiography was performed during general anaesthesia after TVEC (day 0) and on days 1, 2, 6 and then 7 weeks after cardioversion. The two-dimensional (2D) echocardiographic measurements included LA diameter, area and ejection phase indices such as fractional shortening. Atrial TDI measurements included peak myocardial velocity during atrial contraction (A), time to onset A, time to peak A and duration of A.

During follow-up after cardioversion, atrial contractile function measured by 2D echocardiography and TDI gradually improved. At 7 weeks following cardioversion, TDI-based myocardial velocities returned to reference values. However, AF horses still showed significantly larger atrial dimensions, lower 2D ejection phase indices and prolonged TDI-based conduction time compared to the control group. In conclusion, AF-induced atrial contractile dysfunction gradually improves in the weeks following cardioversion, but at 7 weeks post-cardioversion, significant differences remain compared to healthy controls.

Introduction

Atrial fibrillation (AF) is clinically the most important supraventricular dysrhythmia in horses, and in equine athletes performing at maximal capacity AF results in exercise intolerance (Mitten, 1996). In dressage or showjumping horses, clinical signs can be less obvious and diagnosis is often delayed. However, AF has been associated with disproportionate tachycardia, QRS broadening and even R-on-T morphology during exercise, all of which are regarded as potential risk factors for ventricular tachycardia or fibrillation (Verheyen et al., 2012). Treatment is indicated in most AF cases and can be performed using quinidine sulfate (QS) or transvenous electrical cardioversion (TVEC) (Deem and Fregin, 1982; McGurrin et al., 2008).

Although successful cardioversion results in immediate restoration of sinus rhythm, atrial contractile dysfunction can persist longer due to AF-induced atrial remodelling. This has been demonstrated after short (7 days) and long (4–6 months) periods of experimentally-induced AF in horses (van Loon, 2001; De Clercq, 2008a, 2008b). In five horses with naturally occurring AF, atrial contractile dysfunction could be demonstrated at 24–72 h after cardioversion (Schwarzwald et al., 2007a). No data are available on long-term follow-up of atrial function in horses with naturally occurring AF.

Left atrial (LA) function can be divided into three distinct phases. During ventricular systole, the atrium stores pulmonary venous return as a reservoir; during early diastole, the atrium acts as a conduit, and active atrial contraction during late diastole augments left ventricular stroke volume (Blume et al., 2011). Atrial pump function can be quantified non-invasively by two-dimensional (2D) measurements of LA ejection phase indices during atrial contraction, by pulsed wave Doppler of transmitral flow and by tissue Doppler imaging (TDI) (Schwarzwald et al., 2007b). However, optimal alignment with mitral flow is difficult from parasternal images in adult horses (Reef et al., 1989). High frame rate TDI allows quantification of LA myocardial velocity as well as timing of onset and duration of atrial contraction.

The aim of this study was to quantify atrial contractile function and its time course of recovery after cardioversion of naturally occurring AF in horses, using 2D and TDI echocardiography. We hypothesised that atrial contractile dysfunction would be present in the first days after cardioversion and would resolve after 7 weeks follow-up.

* Corresponding author. Tel.: +32 9 264 75 84.
E-mail address: annelies.decloedt@ugent.be (A. Decloedt).

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Materials and methods

Horses

The study population consisted of 42 AF horses without severe valvular regurgitation, comprising 38 Warmbloods, three trotters and one Friesian horse. Four were stallions, 16 geldings and 22 mares. The horses were aged (mean ± SD) 9 ± 4 years, with a bodyweight (BW) of 585 ± 60 kg and a height of 171 ± 7 cm. The three trotter horses were racehorses while the others were used for jumping ($n = 19$), dressage ($n = 9$), recreation ($n = 7$), eventing ($n = 3$) or driving ($n = 1$). Four horses had a previous history of AF. Colour Doppler echocardiography demonstrated mitral regurgitation in 25 horses (9 trivial, 16 mild) and tricuspid regurgitation in 26 horses (14 trivial, 10 mild, 2 moderate). Aortic regurgitation was present in 20 horses (8 trivial, 11 mild and 1 moderate) and pulmonic regurgitation in 15 horses (13 trivial, 2 moderate). The severity of regurgitation was classified based on the area of the regurgitant jet (Reef, 1991).

AF duration was estimated based on history and previous examinations by the local veterinarian. Successful cardioversion was performed using TVEC ($n = 39$) or QS ($n = 3$). TVEC was performed using customised catheters (Rhythm Technologies), following the procedure described previously (De Clercq et al., 2008c). The median number of shocks administered was three (range 1 – 17) with a median total energy applied during the TVEC process of 600 J (125–5580 J) and median energy at conversion 250 J (range 125–360 J). No pre-treatment with amiodarone was performed, but amiodarone (6.52 mg/kg IV over 30 min) was administered during anaesthesia for TVEC to 7/39 horses, either because cardioversion could not be achieved using TVEC alone or because of multiple atrial premature depolarizations after TVEC. For cardioversion using QS, horses were orally treated with 22 mg/kg QS every 2 h through a nasogastric tube until sinus rhythm occurred. One horse converted after two doses, two horses converted after three doses.

The results were compared to 37 healthy horses, consisting of 27 Warmbloods and 10 trotters, of which three were stallions, 15 geldings and 19 were mares. These healthy horses were aged from 8 ± 4 years, with a BW of 552 ± 58 kg and a height of 167 ± 6 cm. Animals with cardiovascular or respiratory disease were excluded based on a general physical examination, thorough cardiac auscultation, 30 min electrocardiogram at rest and routine 2D, M-mode and colour Doppler echocardiography. No murmurs were heard on cardiac auscultation. Doppler echocardiography revealed the presence of trivial mitral regurgitation ($n = 5$), trivial tricuspid regurgitation ($n = 13$), mild tricuspid regurgitation ($n = 3$), trivial aortic regurgitation ($n = 14$) and trivial pulmonic regurgitation ($n = 6$).

Echocardiography

Atrial function was examined on days 1, 2, 6 and then at 7 weeks after cardioversion using a GE Vivid 7 Dimension ultrasound with 3S phased array transducer (GE Healthcare) at 1.7/3.4 MHz. Horses treated by TVEC were additionally examined in left lateral recumbency during general anaesthesia within 15 min following cardioversion (day 0).

Using 2D echocardiography, the left atrium (LA) was imaged from a right parasternal four-chamber and short-axis view (Schwarzwald et al., 2007b). Colour-coded TDI images of the LA free wall were acquired from the right parasternal four-chamber ($LAFW_{4CH}$) and short-axis view (LAsx) and from a left parasternal long-axis view (LLA) (Fig. 1). The interatrial septum was imaged from the four-chamber view ($LASept_{4CH}$). Image orientation was optimised for maximal alignment with atrial wall motion. Greyscale width was reduced to 20°, the TDI sector was narrowed maximally and the velocity scale was set at +16/−16 cm/s. Consequently, a frame rate of 183 frames/s was achieved.

Analysis

Offline analysis was performed using dedicated software (EchoPAC Software v108.1.5, GE Healthcare). Three consecutive cycles were measured separately and averaged subsequently. From the 2D four-chamber view, maximal LA diameter (LAD) was measured as the largest distance parallel to the mitral valve annulus, from the inner edge of the septal wall to the free wall. LA area (LAA) was measured by tracing the inner edge of the atrial wall from the septal to lateral insertion of the mitral valve annulus. LAD and LAA were determined at end ventricular systole ($_{syst}$); onset P ($_p$); maximal atrial contraction ($_a$) and end ventricular diastole ($_{diast}$). From the 2D short-axis view, at end ventricular systole, LA internal dimension ($LA_{sx}D$) and area ($LA_{sx}A$), and aortic internal dimension ($Ao_{sx}D$) and area ($Ao_{sx}A$) were measured, and the ratios of LA and aortic internal dimension ($LA_{sx}D/Ao_{sx}D$) and area ($LA_{sx}A/Ao_{sx}A$) were calculated (Schwarzwald et al., 2007b). LA pump function was quantified by ejection-phase indices: LA fractional shortening FS_{LA} (%) = [(LAD_p − LAD_a)/LAD_p] × 100 and fractional area change FAC_{LA} (%) = [(LAA_p − LAA_a)/LAA_p] × 100 (De Clercq et al., 2008b).

Colour-coded TDI images were analysed using the 'Q-analysis' mode. The sample area (6 × 6 mm) was positioned inside the atrial wall at onset P, at maximal atrial contraction and after atrial relaxation using the anchoring function, in order to track atrial motion throughout the late diastolic phase. A 30 ms temporal smoothing filter was applied. The cine compound function was not used. Measurements were made in the velocity curve (Fig. 1). The RR interval was measured and instantaneous heart rate (HR) was calculated as 60/RR. Measurements included peak atrial contraction velocity (A), time to peak A relative to onset P (tA), time to onset A relative to onset P (onset A) and duration of A (durA). The 0 cm/s velocity level was used as the reference line for peak measurements. Onset and end A were characterised by a sudden change in wall motion seen as a change in sign or amplitude.

Reliability of TDI measurements

Reliability was evaluated in 10 healthy horses by comparing repeated echocardiographic examinations and offline measurements performed by two experienced echocardiographers. All horses were examined by observer 1 on two separate days with a 1 day interval. On one occasion, the examination was repeated by observer 2 immediately before or after observer 1 in a random examination order. Offline analysis was first performed by observer 1 for all exams ($n = 30$). Next, on 1 exam of each horse ($n = 10$), the same three cycles were measured by both observers on a separate occasion. At any time, observers were blinded to echocardiographer, horse, day and any previous results.

Statistics

TDI within-day inter-observer variability was obtained by comparing echocardiographic examinations performed on the same day by observer 1 and 2, both measured by observer 1, in a one-way ANOVA with horse as unit of repeated measure. The coefficients of variation (CV) were calculated by dividing the square root of the mean square error by the grand mean, multiplied by 100 (SPSS Statistics 17.0.1.). In addition, the absolute value below which the difference between two measurements will lie with 95% probability was estimated according to the British Standards Institution recommendations: $1.96 \times \sqrt{2} \times$ the within-subject standard deviation (Schwarzwald et al., 2007b). Similarly, between-day intra-observer variability was determined by comparing examinations recorded on 2 days by observer 1. Measurement variability was obtained by comparing repeated offline measurements of one examination/horse on 2 days (intra-observer measurement variability) or by two observers (inter-observer measurement variability). The degree of repeatability was based on the CV: <15% = low, 15–25% = moderate, >25% = high variability (Schwarzwald et al., 2007b).

Longitudinal analyses of the time course of atrial function recovery after cardioversion were based on a mixed model with time as categorical fixed effect and horses as subjects for repeated measures (SAS v9.3). Results at days 0–6 were compared to 7 weeks after cardioversion using Dunnett's method to adjust for multiple comparisons. The effect of medication and AF duration were tested by adding medication and duration as fixed categorical variables to the mixed model. AF duration was divided in two classes: long (>1 month prior to cardioversion) and short (⩽1 month). For medication, three groups were compared: TVEC without anti-arrhythmic medication, TVEC with amiodarone and cardioversion by QS. Results at 7 weeks after cardioversion were compared to the control group using an independent samples t test. The level of significance was $P < 0.05$.

Results

AF duration was long (median 6 months, range 1.5–24 months) in 35 horses and short (median 25 days, range 10–30 days) in seven horses. All 42 horses were followed up for at least 6 days, although not all measurements could be performed at all the time points (Tables 1 and 3). Twenty-eight horses were followed up at 7 weeks after cardioversion, with a mean follow-up period of 48 ± 9 days except for 2/28 horses that could only be examined after 4 and 8 months. Three horses without a previous history of AF were lost for follow-up because of AF recurrence within 7 weeks after cardioversion, while 11 horses were still in sinus rhythm at 7 weeks after cardioversion but did not return for follow-up echocardiography. Heart rate was significantly higher at day 1 and 2 compared to day 0, 6 and 7 weeks after cardioversion.

LAA measurements were significantly higher at days 1, 2 and 6 compared to 7 weeks after cardioversion (Table 1). Similarly, $LA_{sx}A$ was higher at days 1 and 2. This change of LA size over time was less distinct when evaluating LAD or $LA_{sx}D$. FS_{LA} and FAC_{LA}, were lower at days 0, 1, 2 and 6 compared to 7 weeks after cardioversion. Compared to the control group, all LA size measurements were significantly higher in AF horses at 7 weeks after cardioversion but FS_{LA} and FAC_{LA} were significantly lower.

The CV of TDI measurements are listed in Table 2. All variables showed a low measurement variability, defined as between-day