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Atrial fibrillation in horses part 1: Pathophysiology

Annelies Decloedt[a,*], Glenn Van Steenkiste[a], Lisse Vera[a], Rikke Buhl[b], Gunther van Loon[a]

[a] Equine Cardioteam Gent University, Department of Large Animal Internal Medicine, Faculty of Veterinary Medicine, Ghent University, Belgium
[b] Department of Veterinary Clinical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark

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ABSTRACT

Atrial fibrillation (AF) is the most common clinically relevant arrhythmia in horses, with a reported prevalence up to 2.5%. The pathophysiology has mainly been investigated in experimental animal models and human medicine, with limited studies in horses. Atrial fibrillation results from the interplay between electrical triggers and a susceptible substrate. Triggers consist of atrial premature depolarizations due to altered automaticity or triggered activity, or local (micro)reentry. The arrhythmia is promoted by atrial myocardial ion channel alterations, Ca^{2+} handling alterations, structural abnormalities, and autonomic nervous system imbalance. Predisposing factors include structural heart disease such as valvular regurgitation resulting in chronic atrial stretch, although many horses show so-called 'lone AF' or idiopathic AF in which no underlying cardiac abnormalities can be detected using routine diagnostic techniques. These horses may have underlying ion channel dysfunction or undiagnosed myocardial (micro)structural alterations. Atrial fibrillation itself results in electrical, contractile and structural remodelling, fostering AF maintenance. Electrical remodelling leads to shortening of the atrial effective refractory period, promoting reentry. Contractile remodelling consists of decreased myocardial contractility, while structural remodelling includes the development of interstitial fibrosis and atrial enlargement. Reverse remodelling occurs after cardioversion to sinus rhythm, but full recovery may take weeks to months depending on duration of AF. The clinical signs of AF depend on the aerobic demands during exercise, ventricular rhythm response and presence of underlying cardiac disease. In horses with so-called 'lone AF', clinical signs are usually absent at rest but during exercise poor performance, exercise-induced pulmonary hemorrhage, respiratory distress, weakness or rarely collapse may develop.

Introduction

Atrial fibrillation (AF) is a type of cardiac arrhythmia common in humans, dogs and horses. It is considered the most common pathological arrhythmia causing poor performance in equine athletes (Reef et al., 2014). The reported prevalence in horses ranges from 0.3% to 2.5% depending on the population. The overall frequency of AF on a post-race electrocardiogram (ECG) in Standardbred racehorses was 0.14%, although the frequency increased to 2.0% if only horses with poor performance were considered (Slack et al., 2015). Similarly, the estimated frequency of AF among Thoroughbred racehorses was 0.29% with an estimated prevalence of 1.39% among horses which finished slowly or did not finish (Ohmura et al., 2003). In a mixed-breed hospital-based population of 3434 horses, the prevalence of AF was 2.3% (Leroux et al., 2013). The incidence of AF was reported to be 2.5% in a mixed population of 2477 horses consisting of equine patients (n = 389, AF prevalence 6.2%), army and competition horses (n = 496, 0.8%) and horses examined at an abattoir (n = 1592, 2.2%) (Else and Holmes, 1971).

Atrial fibrillation is defined as a supraventricular tachyarrhythmia characterized by uncoordinated atrial depolarization due to multiple chaotic reentry waves, leading to ineffective atrial mechanical function (January et al., 2014). In humans, AF can be further categorized as paroxysmal, persistent or permanent depending on the duration of the arrhythmia and this terminology is often used in veterinary medicine. Paroxysmal AF spontaneously converts back to sinus rhythm (SR), usually within 24–48 h after AF onset. This can be seen in racehorses with AF onset during intense exercise (Holmes et al., 1986; Ohmura et al., 2003). In most sport horses, AF is sustained and horses are typically presented with persistent AF that requires treatment to cardiovert to SR. Some horses develop permanent AF, which means that it does not respond to treatment.

AF can also be classified by its cause. In so-called 'lone AF', no underlying disease can be detected using routine diagnostic tests (Reef et al., 2014), although mild valvular regurgitation without atrial dilatation is sometimes found in these horses. In human

* Corresponding author.
E-mail address: annelies.decloedt@ugent.be (A. Decloedt).

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medicine, researchers have recommended that the terminology 'lone AF' should be avoided as these patients may have microstructural atrial myocardial abnormalities such as channelopathies or fibrosis (Wyse et al., 2014). Therefore 'idiopathic AF' would be a more correct term. A genetic predisposition has been described in Standardbred racehorses, in which the arrhythmia was found to be particularly prevalent in the descendants of one sire family (Kraus et al., 2017, 2018). Secondly, AF can be caused by underlying cardiac disease. Horses can be predisposed to develop AF following structural heart disease such as valvular insufficiency or congenital defects causing atrial enlargement (Reef et al., 1988). These horses are prone to recurrence if treatment is attempted (Reef et al., 2014).

Atrial fibrillation should be distinguished from focal atrial tachycardia or atrial flutter, which may have similarities in clinical presentation but have a different underlying mechanism. Historically, atrial tachycardia (AT) was defined as the presence of more than three consecutive atrial premature depolarizations while atrial flutter was defined as a single macroreentry wave over a fixed pathway. However, the criteria for differentiating AT and atrial flutter from a surface ECG are not clearly defined in horses. Therefore, it has been proposed to use the general term AT for all rhythms with rapid, regular atrial depolarisations regardless of the causal mechanism (van Loon, 2019; Van Steenkiste et al., 2019). Atrial tachycardia is further subdivided into focal AT when impulses originate from a small, rapidly firing myocardial area (focus) and macroreentrant AT including different types of atrial flutter. In macroreentrant AT, the depolarization wave rotates over the atrial myocardium following a stable pathway around an anatomical or functional area of slow conduction. In-depth characterization of the arrhythmia to identify the underlying mechanism can only be obtained by an advanced electrophysiological study such as electroanatomical mapping.

Initiation of atrial fibrillation

As little information is available about the pathophysiology and underlying mechanisms of AF in horses, most knowledge is extrapolated from experimental studies in animal models and clinical studies in human patients. The electrophysiological basis of AF is an interplay between electrical triggers and a susceptible substrate for reentry (Fig. 1). A crucial factor in the development of AF is functional or structural atrial arrhythmogenic remodelling, which promotes the occurrence of atrial arrhythmias (Nattel and

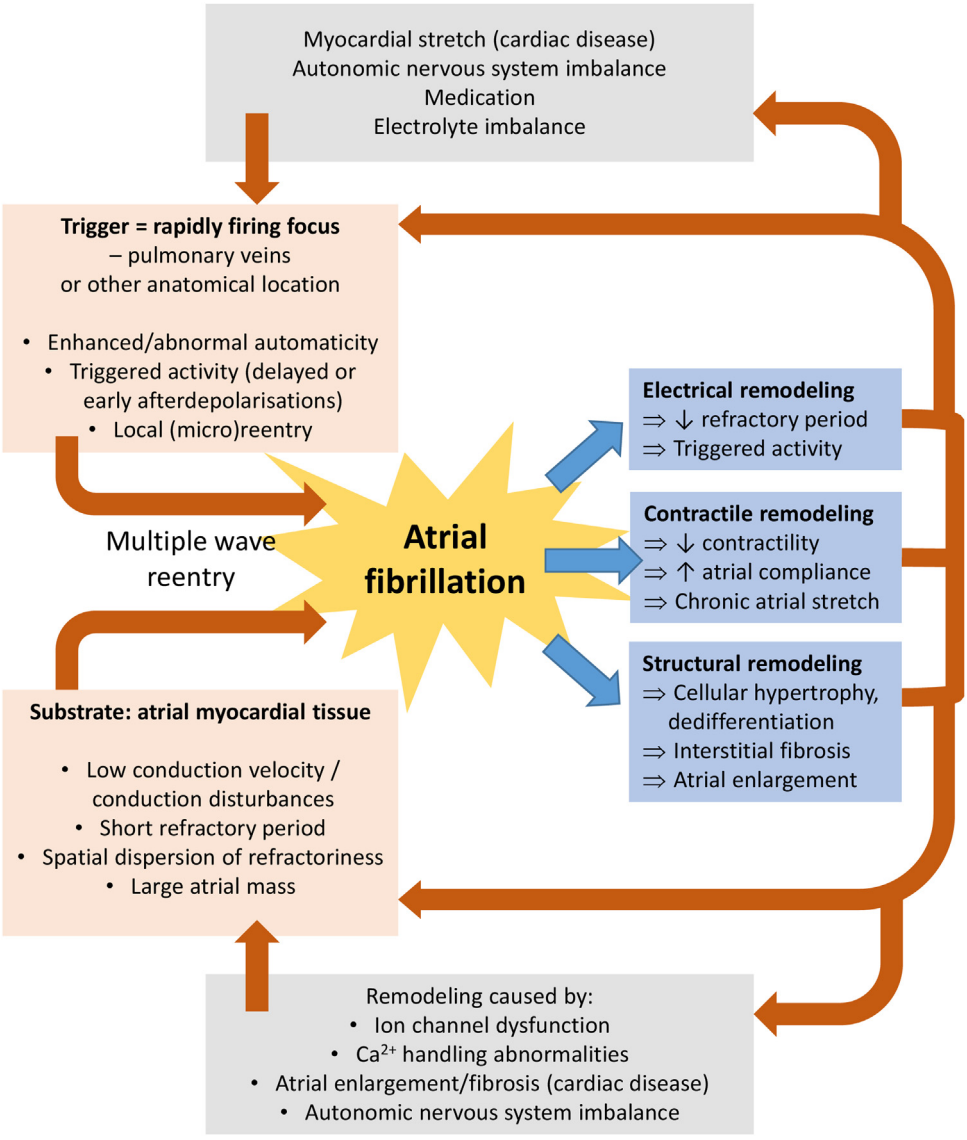

Fig. 1. Schematic overview of the mechanisms of atrial fibrillation.

Harada, 2014). The mechanisms for cellular proarrhythmic remodelling and reentry in the atrial myocardium include ion channel dysfunction, Ca^{2+} handling abnormalities, structural myocardial abnormalities and autonomic nervous system imbalance (Andrade et al., 2014). The initiation of AF may be triggered by the administration of medication such as sodium bicarbonate supplements, thyroid hormones or furosemide resulting in transient potassium depletion (Reef et al., 2014). Atrial fibrillation in itself leads to further electrical, contractile and structural remodelling of the atrial myocardium, resulting in AF maintenance and deterioration of atrial mechanical function. This is often referred to as 'AF domestication' or 'AF begets AF' (Wijffels et al., 1995).

Electrical triggers

Atrial fibrillation is initiated by abnormal electrical activity originating from the atrial myocardium. The atrial action potential is generated by similar ion currents as the ventricular action potential, although the expression of ion channels is slightly different in the atrial compared to the ventricular cardiomyocytes (Schotten et al., 2011). The plateau of the atrial action potential is less pronounced compared to the ventricular action potential, which has also been shown in horses (Fig. 2) (De Clercq et al., 2018). In addition, a large spatial dispersion of the atrial action potential duration was found in experimental studies in other species, which increases the susceptibility to re-entrant arrhythmias (Schotten et al., 2011).

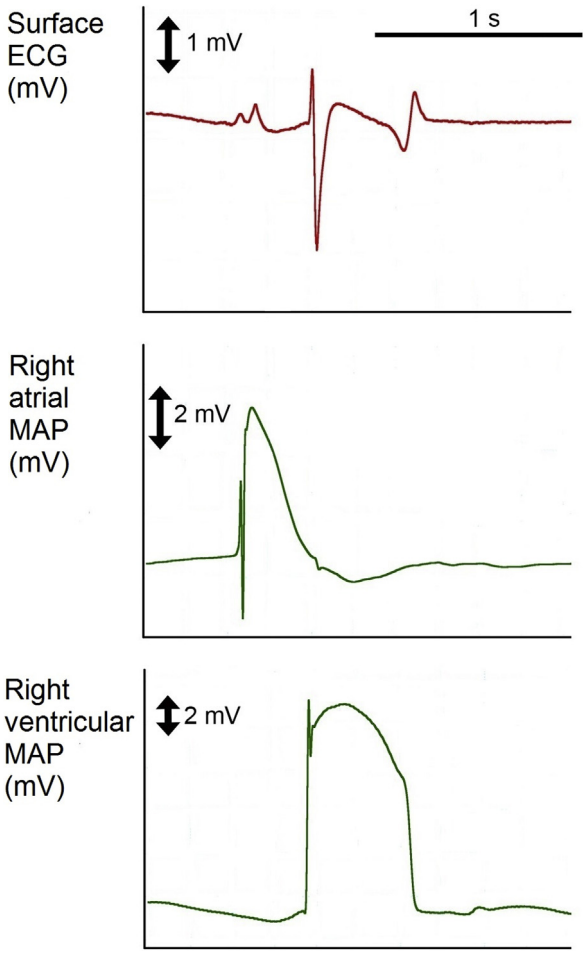

Fig. 2. Surface electrocardiogram (ECG) and right atrial and right ventricular monophasic action potential (MAP) recording at rest in a standing unsedated horse in sinus rhythm.

Atrial premature depolarizations (APDs) are a potential trigger for AF, especially when they occur at very short coupling intervals (van Loon et al., 2000, 2002; Reef et al., 2014). The causal mechanism of these ectopic foci may be either a rapidly firing focus due to enhanced or abnormal automaticity, triggered activity, or local (micro)reentry. Triggered activity results from oscillations of the membrane potential following an action potential. This can be classified as delayed or early afterdepolarizations, occurring after full or partial repolarization of the triggering action potential, respectively (Antzelevitch and Burashnikov, 2011). In human patients, spontaneous rapid ectopic activity often originates from myocardial sleeves in the pulmonary veins (Haissaguerre et al., 1998). These myocardial sleeves have also been identified histologically in the pulmonary veins in horses (Vandecasteele et al., 2018) and one case report has shown spontaneous electrical activity from the pulmonary vein triggering a short run of non-sustained AF during electroanatomical mapping in standing horses (Linz et al., 2020). However, the ectopic foci may also originate from non-pulmonary anatomical locations. Atrial premature depolarizations may also occur as a result of myocardial damage or stretch. During exercise, left atrial pressure increases markedly in horses, causing stretch of the atrial myocardium (Manohar et al., 1993). Due to the heterogeneous anatomical and histological properties of the atrial walls, atrial wall stress is not equally distributed. Areas with high wall stress are probably more susceptible to the development of APDs. In horses, mitral valve regurgitation is well described as an additional risk factor for the development of atrial arrhythmias, as this causes left atrial volume overload, increased left atrial pressures and stretch of the atrial cardiomyocytes (Reef et al., 1998; Trachsel et al., 2013). The same most likely occurs with tricuspid valve regurgitation causing right atrial volume overload and increased right atrial wall stress, although this is probably a less common cause of AF.

Focal AT or macro-reentry AT can also act as a trigger for AF. Atrial tachycardia leads to atrial electrophysiological remodelling and may as such favour the 'deterioration' into sustained AF during which the original triggering focus can no longer be identified. As such, when examining a horse with AF, one cannot determine whether or not the initial trigger was AT. Some horses with AF, however, develop regular AT during a pharmacological or electrical cardioversion attempt. In these cases, focal or macro-reentry AT was most likely the initiating cause of AF (van Loon, 2019). These horses could benefit from targeted ablation of the rapidly firing focus or reentry pathway.

Development of reentry waves

Atrial fibrillation is characterized by multiple reentry waves circling around the atrial myocardium (Waks and Josephson, 2014). Reentry occurs when a propagating impulse does not follow the normal pathway but instead loops back through an alternative circuit and depolarizes the initially excited myocardial tissue after the refractory period has ended. Macroreentry is defined as a large wavefront circling around the entire atrial myocardium or a large proportion of the atria. Microreentry occurs when the reentry wave loops on a small area of myocardial tissue (Markowitz et al., 2019).

Different mechanisms of reentry have been described in experimental studies and in human patients (Schotten et al., 2011). Circus movement reentry (Fig. 3) consists of an electrical wave following a circular pathway, often around an anatomical or functional obstacle, resulting in continuous repetitive propagation of the excitatory wave, reactivating its site of origin (Andrade et al., 2014). The minimal pathlength for circus movement reentry is determined by the wavelength, calculated as the product of the

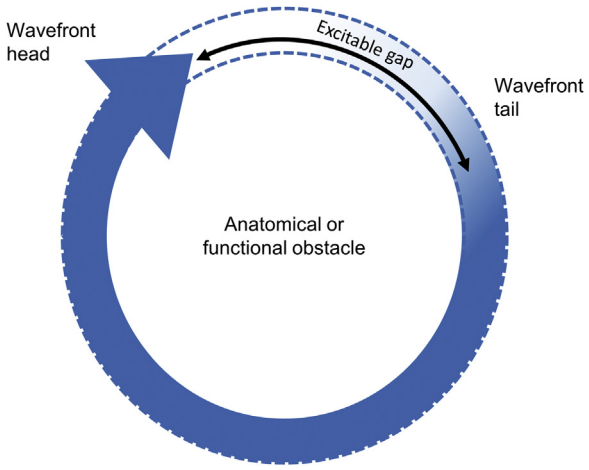

Fig. 3. Schematic representation of circus movement reentry. The electrical wave shows a circular movement, often around an anatomical or functional obstacle and reactivates its site of origin. The circle in dotted lines indicates the pathlength. The blue arrow indicates the wavelength of the depolarisation wave front, which is calculated as the product of the conduction velocity and the atrial effective refractory period. The blue color indicates depolarised myocardial tissue brought in a refractory state, the white color indicates myocardial tissue which has regained full excitability. The pathlength should be longer than the wavelength, with a 'spatial excitable gap' which is defined as the part of the pathway that is excitable due to fully (white) or partially (light blue) recovered myocardium. This excitable gap can be calculated as the product of the conduction velocity and temporal excitable gap (time between recovery of the tissue and re-excitation).

conduction velocity and the atrial effective refractory period (AERP). The pathlength should be longer than the wavelength, resulting in a 'temporal excitable gap' which is defined as the time between recovery of the tissue and re-excitation. The 'spatial excitable gap' is then defined as the part of the pathway consisting of excitable tissue, which can be calculated as the product of the conduction velocity and temporal excitable gap. Reentry can also occur without an anatomical obstacle. According to the 'leading circle concept', the pathway of the electrical wave forms the smallest possible loop in which wave propagation is possible, with a small excitable gap. Other models that have been proposed are spiral wave reentry or rotors as a source of wavelets (Waks and Josephson, 2014). The 'multiple wavelet hypothesis' implies the co-existence of multiple chaotic wavefronts which sustain AF (Moe, 1962). These multiple wavefronts could be the underlying mechanism of AF without localized sources in case of anarchical organization of AF, or could originate from one or more focal sources. Although AF by definition consists of a highly irregular atrial rhythm, it can be maintained by a few individual drivers (Haissaguerre et al., 2014). Remote fibrillatory propagation from focal ectopic sources and multiple wavelet propagation usually follow similar propagation patterns and are therefore hard to distinguish (Benussi and de Maat, 2018).

The perpetuation of AF requires multiple wave reentry, with waves of excitation continuously circling around the atria. New waves originate due to wave division at anatomical structures or refractory tissue, but waves also die out at atrial boundaries or due to wave collision or tissue refractoriness. A critical number of waves is needed for AF to sustain and a high number of wavelets stabilizes AF. The number of reentry circuits coexisting in the atria will be higher in large atria and when the conduction velocity is low and refractory period is short because the latter reduce the reentry wavelength. The necessity of a critical atrial mass for reentry explains why AF is more common in large breed horses or horses with atrial dilatation following valvular regurgitation or structural heart disease. Sustained AF without structural heart disease is rare in small horses, ponies and foals (McGurrin, 2015). Atrial fibrillation perpetuation is also facilitated by heterogeneity in conduction velocity and refractory period.

Autonomic nervous system

The autonomic nervous system may play a role as changes in autonomic balance increase the spatial dispersion of cardiomyocyte refractoriness. This is mainly due to the direct effect on the $I_{K,Ach}$ ion channel. Sympathetic activation by catecholamines also increases the risk of delayed afterdepolarizations by augmenting the intracellular Ca^{2+} concentration (Antzelevitch and Burashnikov, 2011). The role of the autonomic nervous system explains the circadian variation of symptomatic paroxysmal AF in human patients, with events predominantly occurring in the early morning and in the evening (Chen et al., 2014). Horses at rest have a high vagal tone, which has been shown in dogs to increase the dispersion in refractoriness (Alessi et al., 1958). Autonomic imbalance occurs most commonly in horses during exercise or recovery, but could also be induced by tranquilizers or anaesthesia.

In human patients, it has been suggested that epicardial autonomic ganglia in the pulmonary vein region play an important role to trigger AF (Stavrakis et al., 2015). The current ablation strategies for AF treatment might be successful because not only the pulmonary vein myocardial tissue but also the autonomic ganglia at the level of the pulmonary ostia are ablated (Schotten et al., 2011). The histological presence of clustered ganglia at the level of the dorsal left atrial wall and the veno-atrial junction has been confirmed in equine pulmonary vein samples, although their role in the pathogenesis of AF in horses is still unclear (Vandecasteele et al., 2018).

Maintenance of atrial fibrillation: Electrical, contractile and structural remodelling

Atrial fibrillation induces electrical, contractile and structural remodelling which, in turn, favours maintenance of the arrhythmia (Allessie et al., 2002). A pacing-induced AF model in horses has been developed to study atrial remodelling in horses in absence of other cardiac disease (van Loon et al., 2000; van Loon, 2001; van Loon et al., 2002). This model demonstrated atrial remodelling during AF, with reverse remodelling after return to SR (De Clercq et al., 2008, 2019; Hesselkilde et al., 2019).

Electrical remodelling

Electrical remodelling during AF consists of shortening of the AERP and decreased AERP rate adaptation, allowing more wavelets to coexist in the atrial myocardium. This further stabilizes the arrhythmia. The main components of electrical remodelling identified in experimental animal models and humans include decreased L-type Ca^{2+} channel expression, upregulation of the inward rectifier background current I_{K1}, upregulation of the small conductance Ca^{2+} activated K^+ channel expression and remodelling of the gap junction connexin hemichannels (Yue et al., 1999; Nattel and Harada, 2014; Liu et al., 2020). In addition, alterations of intracellular Ca^{2+} handling caused by AF-induced remodelling result in enhanced triggered activity, which may reinitiate AF in case of spontaneous cardioversion. The signalling systems responsible for electrical remodelling include Ca^{2+} signalling and the production of microRNAs which negatively regulate target genes (Nattel and Harada, 2014; Larupa Santos et al., 2020).

Electrical remodelling acts as an acute homeostatic protective mechanism against intracellular Ca^{2+} overload due to the high atrial activation rate by decreasing Ca^{2+} influx and increasing Ca^{2+} efflux. However, this shortens the action potential duration and AERP, which promotes reentry and stabilizes the arrhythmia. In

horses, shortening of the AERP and an attenuation of AERP rate adaptation has been demonstrated by programmed electrical stimulation within the first 24–48 h after the experimental induction of AF by a burst pacing protocol (van Loon, 2001; De Clercq et al., 2008, 2019).

The atrial fibrillation cycle length (AFCL) has been used in horses as an alternative measure of atrial electrical remodelling. Due to the small excitable gap in AF, the AFCL is related to the AERP. The atrial fibrillation cycle length can be measured invasively by an intra-atrial electrogram (Fig. 4) or non-invasively using tissue Doppler imaging (Decloedt et al., 2014) or by measuring the atrial fibrillatory rate (AFR) derived from surface ECG (Hesselkilde et al., 2017). Increased estimated AF duration was associated with shorter AFCL in horses with naturally-occurring AF (De Clercq et al., 2014). In a chronic experimental AF model in horses, the AFR derived by computer-assisted calculation from the surface ECG was used as a marker of electrical remodelling (Hesselkilde et al., 2019). The AFR significantly increased over a two-month period of induced AF, however, no significant alterations of ion channel expression were observed. The latter finding might be due to the small number of animals included in the study.

The underlying mechanisms for electrical remodelling during AF in horses have not yet been completely elucidated. Although the presence of several ion channels and gap junction connexin hemichannels in the equine atrial myocardium has been characterized, the mechanism of remodelling during AF is still unclear (Vandevelde et al., 2016; Hesselkilde et al., 2019).

Contractile remodelling

The left atrial mechanical function consists of three distinct phases (Blume et al., 2011). The left atrium acts as a 'reservoir' during ventricular systole, collecting and storing the incoming pulmonary venous return. The left atrial reservoir function is largely dependent on atrial compliance, which can be decreased in the case of structural remodelling and fibrosis. During the early phase of ventricular diastole, the left atrium acts as a conduit, passively emptying into the left ventricle. Finally, the atrial 'booster function' during late diastole consists of active contraction, augmenting the left ventricular stroke volume. In human patients, this accounts for approximately 15–30 % of left ventricular filling under resting conditions (Lang et al., 2015). In experimentally induced AF in horses, the stroke volume at rest decreased on average by 22%, while the heart rate at rest increased (Kubo et al., 1975).

Atrial mechanical function is impaired as a consequence of sustained atrial fibrillation. The reduced function results from the shortened action potential duration, reduced inward Ca^{2+} current and the alterations of intracellular Ca^{2+} handling and myofilament protein phosphorylation (Wakili et al., 2010). The loss of atrial contractile function increases atrial compliance, leading to dilatation (Schotten et al., 2004) which further stabilizes AF. In experimentally-induced AF in horses, the contractile function measured by echocardiography decreased within the first days after onset of AF, both in a short-term experimental model (De Clercq et al., 2008) as well as in long-term experimental models (van Loon, 2001; De Clercq et al., 2019; Hesselkilde et al., 2019).

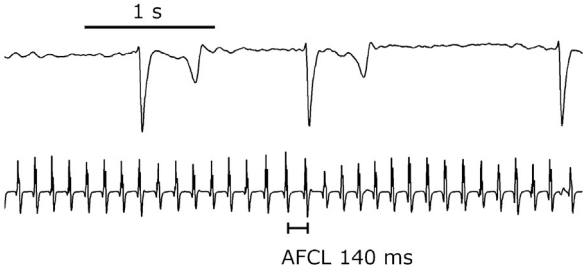

Fig. 4. Surface electrocardiogram (ECG) (upper trace) and right atrial intracardiac electrogram recording (lower trace) recorded at rest in a standing unsedated horse with atrial fibrillation. The atrial fibrillation cycle length (AFCL) can be measured from the right atrial electrogram as the time interval between two successive atrial depolarisations, as indicated by the black line (AFCL 140 ms corresponding to a fibrillatory rate of 428/min).

In human medicine, an important clinical consequence of AF is the risk of thromboembolism. This is caused by atrial mechanical dysfunction due to contractile remodelling, resulting in low blood flow velocity in the atria, combined with other factors such as atrial endothelial damage and dysfunction, increased atrial size and inflammation. In horses with AF, no clinical signs of hypercoagulation or thromboembolism have been described although subclinical activated coagulation has been demonstrated based on standard coagulation tests (Navas de Solis et al., 2016).

Structural remodelling

Structural remodelling includes atrial enlargement and structural changes such as cardiomyocyte dedifferentiation and development of interstitial fibrosis (Ausma et al., 1997; Burstein and Nattel, 2008). Atrial dilatation promotes AF by maintaining reentry, while fibrosis causes local conduction disturbances and may have pro-arrhythmogenic effects. A short-term (seven days) period of experimentally-induced AF did not result in an increase of left atrial size (De Clercq et al., 2008). In contrast, in a chronic AF model the atrial dimensions did enlarge over time (van Loon, 2001; De Clercq et al., 2019; Hesselkilde et al., 2019). In addition, increased amounts of collagen were found in the atrial myocardium after a two-month AF period (Hesselkilde et al., 2019). In a study of experimentally induced AF in horses of one month duration, a significantly increased number of fibroblasts, which are the precursor cells for fibrosis, was observed in both left and right atrium. In addition, capillary density decreased following AF which is indicative of metabolic hypoxia-induced remodelling (Fenner, 2019).

Reverse remodelling after cardioversion

Depending on the AF duration, the electrical, contractile and structural atrial remodelling are reversible and reverse remodelling takes place after cardioversion to sinus rhythm. The electrical properties of the atrial myocardium recover more rapidly than the contractile function, which indicates that the loss of atrial mechanical function is not only associated with the decreased L-type Ca^{2+} channel expression (Schotten et al., 2011). The reversibility of structural myocardial remodelling has only been described to a limited extent in animal models (Everett et al., 2000). Electrical and contractile reverse remodelling have been extensively investigated in both experimentally-induced and naturally-occurring AF in horses. In a chronic (six months) AF model in ponies, the electrophysiological values normalized within 10 days after cardioversion while atrial dimensions and contractile function gradually returned to baseline values over one to two months (van Loon, 2001). After a four-month period of experimentally-induced AF, atrial contractile function returned to baseline within one to two months of sinus rhythm (De Clercq et al., 2019). Reverse remodelling takes less time after a shorter AF period. The atrial effective refractory period shortening and loss of atrial mechanical function after a seven day experimentally-induced AF episode resolved within 24–48 h after cardioversion (De Clercq et al., 2008).

At 24 h after cardioversion of naturally-occurring AF, the atrial contractile function was markedly decreased (Schwarzwald et al.,

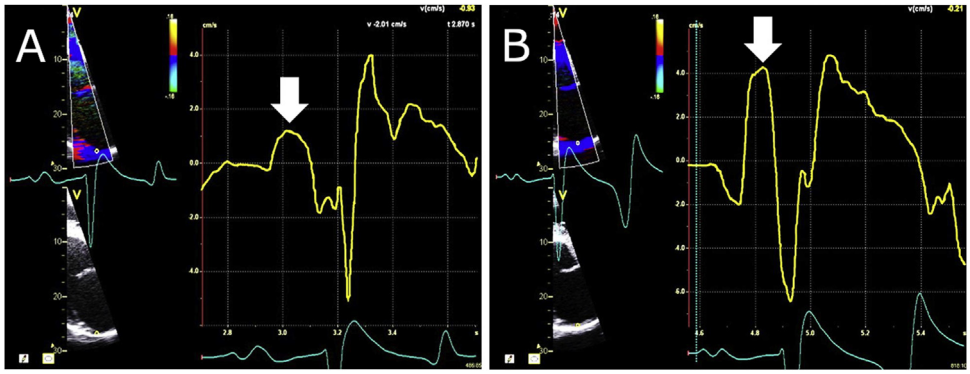

Fig. 5. Two tissue Doppler velocity curves of the left atrial free wall from a right parasternal four chamber view from the same horse. On each panel, the tissue Doppler image on the left shows the position of the sample area in the left atrial myocardium. The white arrow on the tissue Doppler curve on the right indicates the peak myocardial velocity during atrial contraction. (A) One day after cardioversion, low myocardial velocity indicates incomplete reverse contractile remodelling. (B) Seven weeks after cardioversion, normal myocardial velocity indicates complete reverse contractile remodelling.

2007). The atrial mechanical function was significantly improved at 72 h after cardioversion. The rather quick recovery in this study might be associated with the short duration of AF, as most horses had AF for less than 10 days. As 4/5 horses were converted using quinidine sulphate, residual drug effects could be partially responsible for the impaired atrial contractile function at 24 h after cardioversion. The effect of treatment modality on atrial function is unclear and some studies in human medicine demonstrated more prolonged and severe atrial dysfunction after electrical cardioversion (Harjai et al., 1997). In horses with persistent spontaneous AF, the left atrial peak myocardial velocity during active atrial contraction returned to normal values at 7 weeks after electrical cardioversion (Fig. 5) (Decloedt et al., 2013). Remarkably, the atrial fractional shortening and fractional area change remained significantly lower compared to healthy control horses, even at 7 weeks after cardioversion. Although this might indicate incomplete reverse remodelling of contractile function or presence of fibrosis, it could also be associated with the larger atrial dimensions in AF horses. It is unclear whether this atrial enlargement is also a consequence of atrial remodelling due to AF or whether this was the cause of AF.

Cardiac function and clinical signs

Cardiac function is impaired in horses with AF due to the rapid and irregular rate of atrial activation (usually around 350/min or more) and atrial contractile remodelling resulting in atrial contractile dysfunction and reduced ventricular filling. This may result in a reduction in the left ventricular fractional shortening and a decrease in the left ventricular ejection time measured by echocardiography (Marr et al., 1995). These signs of left ventricular dysfunction usually disappear after cardioversion. The atrioventricular (AV) node plays a crucial role in determining the hemodynamic effects of AF and the associated clinical signs. As horses have a high vagal tone at rest, most atrial impulses are blocked by the AV node by a long AV nodal refractoriness and the mean ventricular rate remains normal (Hamlin et al., 1972; Reef et al., 2014). Reduced ventricular filling due to atrial mechanical dysfunction is largely compensated by the long diastolic interval at low heart rates (Muir and McGuirk, 1984). Therefore, horses with 'lone AF' usually show no clinical signs at rest, although some owners report subtle behavioural changes when AF occurs. In horses with AF and high resting heart rates, the possible presence of an accessory bypass tract should be considered (Jesty et al., 2011).

During exercise or stress, the sympathetic tone increases resulting in a shortened AV nodal refractory period and enhanced AV conduction. In horses with AF, a disproportionate ventricular response rate develops with heart rates which are 40–60 beats/min higher than expected for the workload (Buntenkotter and Deegen, 1976; Verheyen et al., 2013; Buhl et al., 2018). The high heart rates combined with the absence of active atrial contraction result in impaired cardiac output. In addition, the authors have observed pronounced ventricular dyssynchrony in some horses by echocardiography during these periods of high cardiac frequency, which again impairs cardiac function. Some horses also present abnormal QRS morphology and R-on-T phenomenon (Verheyen et al., 2013; Buhl et al., 2018). Although the abnormal QRS morphology might be associated with ventricular ectopy, it is probably supraventricular in origin with aberrant conduction in the ventricles due to the high heart rate.

Depending on the aerobic demands during exercise, the presence of AF may or may not result in clinical signs. Horses working at submaximal intensity such as horses used for recreational purposes or disciplines such as dressage may show no or only subtle clinical signs if the heart rate remains relatively low during exercise. As such, AF is often detected by coincidence in these horses and they usually present with chronic AF. Racehorses or horses competing in physically challenging disciplines such as eventing may show a range of clinical signs such as poor performance, exercise-induced pulmonary hemorrhage, acute pulmonary oedema, respiratory distress or prolonged recovery after exercise. In case of acute AF onset during exercise, the sudden decrease in cardiac output may cause affected horses to decelerate immediately, sometimes associated with a brief episode of incoordination or distress. However, paroxysmal AF may also go unnoticed, even in racehorses (Slack et al., 2015). However, the high heart rates, aberrant ventricular conduction and ventricular dyssynchrony have been associated with collapse or rarely even sudden death (Lyle et al., 2010; Young and van Loon, 2014; van Loon, 2019).

In horses with congestive heart failure, the acute onset of AF is usually associated with a sudden deterioration of the clinical status. These horses already show a high sympathetic tone caused by the gradual development of congestive heart failure. The onset of AF leads to a sudden increase in heart rate with reduced ventricular filling, impaired cardiac output and augmented atrial pressures, which results in the sudden development of overt clinical signs at rest (van Loon, 2019).

Conclusions

Atrial fibrillation is the most common clinically important arrhythmia in equine athletes. Atrial fibrillation develops as a

consequence of focal ectopic firing combined with a reentry maintaining substrate. Timely treatment is indicated as the arrhythmia itself causes electrical, contractile and structural remodelling which promotes maintenance of atrial fibrillation. The time for reverse remodelling depends on the AF duration. Experimental studies suggest that chronic AF may be associated with myocardial fibrosis.

Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

References

Alessi, R., Nusynowitz, M., Abildskov, J.A., Moe, G.K., 1958. Nonuniform distribution of vagal effects on the atrial refractory period. Am. J. Physiol. 194, 406–410.

Allessie, M., Ausma, J., Schotten, U., 2002. Electrical, contractile and structural remodeling during atrial fibrillation. Cardiovasc. Res. 54, 230–246.

Andrade, J., Khairy, P., Dobrev, D., Nattel, S., 2014. The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. Circ. Res. 114, 1453–1468.

Antzelevitch, C., Burashnikov, A., 2011. Overview of basic mechanisms of cardiac arrhythmia. Card. Electrophysiol. Clin. 3, 23–45.

Ausma, J., Wijffels, M., Thone, F., Wouters, L., Allessie, M., Borgers, M., 1997. Structural changes of atrial myocardium due to sustained atrial fibrillation in the goat. Circulation 96, 3157–3163.

Benussi, S., de Maat, G.E., 2018. Atrial remodelling and function: implications for atrial fibrillation surgery. Eur. J. Cardio-thoracic Surg. 53, 2–8.

Blume, G.G., McLeod, C.J., Barnes, M.E., Seward, J.B., Pellikka, P.A., Bastiansen, P.M., Tsang, T.S., 2011. Left atrial function: physiology, assessment, and clinical implications. Eur. J. Echocardiogr. 12, 421–430.

Buhl, R., Carstensen, H., Hesselkilde, E.Z., Klein, B.Z., Hougaard, K.M., Ravn, K.B., Loft-Andersen, A.V., Fenner, M.F., Pipper, C., Jespersen, T., 2018. Effect of induced chronic atrial fibrillation on exercise performance in Standardbred trotters. J. Vet. Intern. Med. 32, 1410–1419.

Buntenkotter, S., Deegen, E., 1976. Behaviour of the heart rate of horses with auricular fibrillation during exercise and after treatment. Equine Vet. J. 8, 26–29.

Burstein, B., Nattel, S., 2008. Atrial fibrosis: mechanisms and clinical relevance in atrial fibrillation. J. Am. Coll. Cardiol. 51, 802–809.

Chen, P.S., Chen, L.S., Fishbein, M.C., Lin, S.F., Nattel, S., 2014. Role of the autonomic nervous system in atrial fibrillation: pathophysiology and therapy. Circ. Res. 114, 1500–1515.

De Clercq, D., van Loon, G., Tavernier, R., Duchateau, L., Deprez, P., 2008. Atrial and ventricular electrical and contractile remodeling and reverse remodeling owing to short-term pacing-induced atrial fibrillation in horses. J. Vet. Intern. Med. 22, 1353–1359.

De Clercq, D., Decloedt, A., Sys, S.U., Verheyen, T., Van der Vekens, N., van Loon, G., 2014. Atrial fibrillation cycle length and atrial size in horses with and without recurrence of atrial fibrillation after electrical cardioversion. J. Vet. Intern. Med. 28, 624–629.

De Clercq, D., Broux, B., Vera, L., Decloedt, A., van Loon, G., 2018. Measurement variability of right atrial and ventricular monophasic action potential and refractory period measurements in the standing non-sedated horse. BMC Vet. Res. 14, 101.

De Clercq, D., Decloedt, A., Tavernier, R., Deprez, P., van Loon, G., 2019. Atrial and ventricular electrical and contractile remodelling and reverse remodelling due to chronic pacing-induced atrial fibrillation in horses: preliminary results. Vlaams Tijdschr. 88, 269–277.

Decloedt, A., Verheyen, T., Van Der Vekens, N., Sys, S., De Clercq, D., van Loon, G., 2013. Long-term follow-up of atrial function after cardioversion of atrial fibrillation in horses. Vet. J. 197, 583–588.

Decloedt, A., de Clercq, D., van der Vekens, N., Verheyen, T., van Loon, G., 2014. Noninvasive determination of atrial fibrillation cycle length by atrial colour tissue Doppler imaging in horses. Equine Vet. J. 46, 174–179.

Else, R.W., Holmes, J.R., 1971. Pathological changes in atrial fibrillation in the horse. Equine Vet. J. 3, 56–64.

Everett, T.H., Li, H., Mangrum, J.M., McRury, I.D., Mitchell, M.A., Redick, J.A., Haines, D.E., 2000. Electrical, morphological, and ultrastructural remodeling and reverse remodeling in a canine model of chronic atrial fibrillation. Circulation 102, 1454–1460.

Fenner, M.F., 2019. An Equine Model for Persistent Atrial Fibriallation. Translational Thoughts on Novel Atrial Selective Targets and Cardiac Remodelling in Atrial Fibrillation. Thesis, PhD in Veterinary Sciences, University of Copenhagen, Denmark. , pp. 41–48.

Haissaguerre, M., Jais, P., Shah, D.C., Takahashi, A., Hocini, M., Quiniou, G., Garrigue, S., Le Mouroux, A., Le Metayer, P., Clementy, J., 1998. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N. Engl. J. Med. 339, 659–666.

Haissaguerre, M., Hocini, M., Denis, A., Shah, A.J., Komatsu, Y., Yamashita, S., Daly, M., Amraoui, S., Zellerhoff, S., Picat, M.Q., et al., 2014. Driver domains in persistent atrial fibrillation. Circulation 130, 530–538.

Hamlin, R.L., Gilpin, K.W., Smith, C.R., Klepinger, W.L., 1972. Autonomic control of heart-rate in horse. Am. J. Physiol. 222, 3.

Harjai, K.J., Mobarek, S.K., Cheirif, J., Boulos, L.M., Murgo, J.P., Abi-Samra, F., 1997. Clinical variables affecting recovery of left atrial mechanical function after cardioversion from atrial fibrillation. J. Am. Coll. Cardiol. 30, 481–486.

Hesselkilde, E.Z., Carstensen, H., Haugaard, M.M., Carlson, J., Pehrson, S., Jespersen, T., Buhl, R., Platonov, P.G., 2017. Effect of flecainide on atrial fibrillatory rate in a large animal model with induced atrial fibrillation. BMC Cardiovasc. Disord. 17, 289.

Hesselkilde, E.Z., Carstensen, H., Flethoj, M., Fenner, M., Kruse, D.D., Sattler, S.M., Tfelt-Hansen, J., Pehrson, S., Braunstein, T.H., Carlson, J., et al., 2019. Longitudinal study of electrical, functional and structural remodelling in an equine model of atrial fibrillation. BMC Cardiovasc. Disord. 19, 228.

Holmes, J.R., Henigan, M., Williams, R.B., Witherington, D.H., 1986. Paroxysmal atrial fibrillation in racehorses. Equine Vet. J. 18, 37–42.

January, C.T., Wann, L.S., Alpert, J.S., Calkins, H., Cigarroa, J.E., Cleveland Jr., J.C., Conti, J.B., Ellinor, P.T., Ezekowitz, M.D., Field, M.E., et al., 2014. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J. Am. Coll. Cardiol. 64, e1–76.

Jesty, S.A., Kraus, M.S., Johnson, A.L., Gelzer, A.R., Bartol, J., 2011. An accessory bypass tract masked by the presence of atrial fibrillation in a horse. J. Vet. Cardiol. 13, 79–83.

Kraus, M., Physick-Sheard, P.W., Brito, L.F., Schenkel, F.S., 2017. Estimates of heritability of atrial fibrillation in the Standardbred racehorse. Equine Vet. J. 49, 718–722.

Kraus, M., Physick-Sheard, P., Brito, L.F., Sargolzaei, M., Schenkel, F.S., 2018. Marginal ancestral contributions to atrial fibrillation in the Standardbred racehorse: comparison of cases and controls. PLoS One 13, e0197137.

Kubo, K., Senta, T., Sugimoto, O., 1975. Changes in cardiac output with experimentally induced atrial fibrillation in the horse. Experimental Reports of Equine Health Laboratory 12, 101–106.

Lang, R.M., Badano, L.P., Mor-Avi, V., Afilalo, J., Armstrong, A., Ernande, L., Flachskampf, F.A., Foster, E., Goldstein, S.A., Kuznetsova, T., et al., 2015. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J. Am. Soc. Echocardiogr. 28 (1–39), e14.

Larupa Santos, J., Rodriguez, I., Olesen, M.S., Hjorth Bentzen, B., Schmitt, N., 2020. Investigating gene-microRNA networks in atrial fibrillation patients with mitral valve regurgitation. PLoS One 15, e0232719.

Leroux, A.A., Detilleux, J., Sandersen, C.F., Borde, L., Houben, R.M., Al Haidar, A., Art, T., Amory, H., 2013. Prevalence and risk factors for cardiac diseases in a hospital-based population of 3,434 horses (1994-2011). J. Vet. Intern. Med. 27, 1563–1570.

Linz, D., Hesselkilde, E.Z., Kutieleh, R., Jespersen, T., Buhl, R., Sanders, P., 2020. Pulmonary vein firing initiating atrial fibrillation in the horse: oversized dimensions but similar mechanisms. J. Cardiovasc. Electrophysiol. 31, 1211–1212.

Liu, T., Xiong, F., Qi, X.Y., Xiao, J., Villeneuve, L., Abu-Taha, I., Dobrev, D., Huang, C., Nattel, S., 2020. Altered calcium handling produces reentry-promoting action potential alternans in atrial fibrillation-remodeled hearts. Journal of Clinical Investigation Insight 5, e133754.

Lyle, C.H., Turley, G., Blissitt, K.J., Pirie, R.S., Mayhew, I.G., McGorum, B.C., Keen, J.A., 2010. Retrospective evaluation of episodic collapse in the horse in a referred population: 25 cases (1995-2009). J. Vet. Intern. Med. 24, 1498–1502.

Manohar, M., Hutchens, E., Coney, E., 1993. Pulmonary hemodynamics in the exercising horse and their relationship to exercise-induced pulmonary hemorrhage. Br. Vet. J. 149, 419–428.

Markowitz, S.M., Thomas, G., Liu, C.F., Cheung, J.W., Ip, J.E., Lerman, B.B., 2019. Atrial tachycardias and atypical atrial flutters: mechanisms and approaches to ablation. Arrhythm. Electrophysiol. Rev. 8, 131–137.

Marr, C.M., Reef, V.B., Reimer, J.M., Sweeney, R.W., Reid, S.W., 1995. An echocardiographic study of atrial fibrillation in horses: before and after conversion to sinus rhythm. J. Vet. Intern. Med. 9, 336–340.

McGurrin, M.K.J., 2015. The diagnosis and management of atrial fibrillation in the horse. Vet. Med. Res. Rep. 6, 83–90.

Moe, G.K., 1962. On multiple wavelet hypothesis of atrial fibrillation. Arch. Int. Pharmacodyn. Ther. 140, 183–188.

Muir, W.W., McGuirk, S.M., 1984. Hemodynamics before and after conversion of atrial fibrillation to normal sinus rhythm in horses. J. Am. Vet. Med. Assoc. 184, 965–970.

Nattel, S., Harada, M., 2014. Atrial remodeling and atrial fibrillation. J. Am. Coll. Cardiol. 63, 2335–2345.

Navas de Solis, C., Reef, V.B., Slack, J., Jose-Cunilleras, E., 2016. Evaluation of coagulation and fibrinolysis in horses with atrial fibrillation. J. Am. Vet. Med. Assoc. 248, 201–206.

Ohmura, H., Hiraga, A., Takahashi, T., Kai, M., Jones, J.H., 2003. Risk factors for atrial fibrillation during racing in slow-finishing horses. J. Am. Vet. Med. Assoc. 223, 84–88.

Reef, V.B., Levitan, C.W., Spencer, P.A., 1988. Factors affecting prognosis and conversion in equine atrial fibrillation. J. Vet. Intern. Med. 2, 1–6.

Reef, V.B., Bain, F.T., Spencer, P.A., 1998. Severe mitral regurgitation in horses: clinical, echocardiographic and pathological findings. Equine Vet. J. 30, 18–27.
Reef, V.B., Bonagura, J., Buhl, R., McGurrin, M.K., Schwarzwald, C.C., van Loon, G., Young, L.E., 2014. Recommendations for management of equine athletes with cardiovascular abnormalities. J. Vet. Intern. Med. 28, 749–761.
Schotten, U., de Haan, S., Neuberger, H.R., Eijsbouts, S., Blaauw, Y., Tieleman, R., Allessie, M., 2004. Loss of atrial contractility is primary cause of atrial dilatation during first days of atrial fibrillation. Am. J. Physiol. Heart Circ. Physiol. 287, H2324–2331.
Schotten, U., Verheule, S., Kirchhof, P., Goette, A., 2011. Pathophysiological mechanisms of atrial fibrillation: a translational appraisal. Physiol. Rev. 91, 265–325.
Schwarzwald, C.C., Schober, K.E., Bonagura, J.D., 2007. Echocardiographic evidence of left atrial mechanical dysfunction after conversion of atrial fibrillation to sinus rhythm in 5 horses. J. Vet. Intern. Med. 21, 820–827.
Slack, J., Boston, R.C., Soma, L.R., Reef, V.B., 2015. Occurrence of cardiac arrhythmias in Standardbred racehorses. Equine Vet. J. 47, 398–404.
Stavrakis, S., Nakagawa, H., Po, S.S., Scherlag, B.J., Lazzara, R., Jackman, W.M., 2015. The role of the autonomic ganglia in atrial fibrillation. J. Am. Coll. Cardiol. 1, 1–13.
Trachsel, D.S., Schwarzwald, C.C., Bitschnau, C., Grenacher, B., Weishaupt, M.A., 2013. Atrial natriuretic peptide and cardiac troponin I concentrations in healthy Warmblood horses and in Warmblood horses with mitral regurgitation at rest and after exercise. J. Vet. Cardiol. 15, 105–121.
van Loon, G., 2001. Atrial Pacing and Experimental Atrial Fibrillation in Equines. Thesis, PhD in Veterinary Sciences, Ghent University, Belgium. , pp. 161–206.
van Loon, G., 2019. Cardiac arrhythmias in horses. Veterinary Clinics of North America – Equine Practice 35, 85–102.
van Loon, G., Tavernier, R., Duytschaever, M., Fonteyne, W., Deprez, P., Jordaens, L., 2000. Pacing induced sustained atrial fibrillation in a pony. Can. J. Vet. Res. 64, 254–258.
van Loon, G., Duytschaever, M., Tavernier, R., Fonteyne, W., Jordaens, L., Deprez, P., 2002. An equine model of chronic atrial fibrillation: methodology. Vet. J. 164, 142–150.
Van Steenkiste, G., De Clercq, D., Vera, L., Decloedt, A., van Loon, G., 2019. Sustained atrial tachycardia in horses and treatment by transvenous electrical cardioversion. Equine Vet. J. 51, 634–640.
Vandecasteele, T., Van Den Broeck, W., Tay, H., Couck, L., van Loon, G., Cornillie, P., 2018. 3D reconstruction of the porcine and equine pulmonary veins, supplemented with the identification of telocytes in the horse. Anat. Histol. Embryol. 47, 145–152.
Vandevelde, K., Van den Broeck, W., Wang, N., Vandecasteele, T., van Loon, G., 2016. Connexins in the Horse Heart. European Association of Veterinary Anatomists Congress, Vienna, Austria.
Verheyen, T., Decloedt, A., van der Vekens, N., Sys, S., De Clercq, D., van Loon, G., 2013. Ventricular response during lungeing exercise in horses with lone atrial fibrillation. Equine Vet. J. 45, 309–314.
Wakili, R., Yeh, Y.H., Yan Qi, X., Greiser, M., Chartier, D., Nishida, K., Maguy, A., Villeneuve, L.R., Boknik, P., Voigt, N., et al., 2010. Multiple potential molecular contributors to atrial hypocontractility caused by atrial tachycardia remodeling in dogs. Circ. Arrhythm. Electrophysiol. 3, 530–541.
Waks, J.W., Josephson, M.E., 2014. Mechanisms of atrial fibrillation - reentry, rotors and reality. Arrhythm. Electrophysiol. Rev. 3, 90–100.
Wijffels, M.C., Kirchhof, C.J., Dorland, R., Allessie, M.A., 1995. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation 92, 1954–1968.
Wyse, D.G., Van Gelder, I.C., Ellinor, P.T., Go, A.S., Kalman, J.M., Narayan, S.M., Nattel, S., Schotten, U., Rienstra, M., 2014. Lone atrial fibrillation: Does it exist? J. Am. Coll. Cardiol. 63, 1715–1723.
Young, L., van Loon, G., 2014. Diseases of the heart and vessels, Equine Sports Medicine and Surgery. second edn. Saunders Elsevier, St. Louis, MO, USA, pp. 695–743.
Yue, L., Melnyk, P., Gaspo, R., Wang, Z., Nattel, S., 1999. Molecular mechanisms underlying ionic remodeling in a dog model of atrial fibrillation. Circ. Res. 84, 776–784.