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# **EQUINE ELECTROCARDIOGRAPHY: EXPLORATION OF NEW DIAGNOSTIC STRATEGIES**

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Equine electrocardiography: exploration of new diagnostic strategies

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**“He who maintains that new knowledge of electrocardiography is no longer possible, ignores history”**

Dr. Charles Fisch



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# LIST OF ABBREVIATIONS

2DST	two-dimensional speckle tracking
AERP	atrial effective refractory period
AFCL	atrial fibrillation cycle length
$A_m$	peak radial wall motion velocity during late diastole
AM	atypical myopathy
Ao	aortic diameter
APD	atrial premature depolarisation
AV	atrioventricular
CD	contraction duration by TDI
CD <sub>SC</sub>	time to peak circumferential strain
CD <sub>SL</sub>	time to peak longitudinal strain
CD <sub>SR</sub>	time to peak radial strain
CK	creatine kinase
cTnI	cardiac troponin I
DHA	docosahexaenoic acid
E	early diastolic filling
EAD	early afterdepolarisation
ECG	electrocardiogram
E/E <sub>10/20/30</sub>	intra-esophageal recording with interelectrode distance of 10, 20 or 30 cm
$E_m$	peak radial wall motion velocity during early diastole
E/S <sub>high/mid/low</sub>	combined esophageal-surface recording with surface electrode positioned high, mid or low
FS	fractional shortening
HW	height at the withers
IVRT	isovolumic relaxation time
IVS	interventricular septum
MADD	multiple acyl-CoA dehydrogenase deficiency
mSR	maintenance of sinus rhythm
LLA	left atrial diameter measured from a left parasternal view
LA <sub>sa</sub>	left atrial internal diameter measured from a short axis view

LVFW	left ventricular free wall
LVPEP	left ventricular pre-ejection period
LVET	left ventricular ejection time
LQTS	long QT syndrome
MEA	mean electrical axis
p5	5 <sup>th</sup> percentile
P/QRS <sub>magn</sub>	ratio of P wave magnitude and QRS complex magnitude
PSM	postsystolic motion
rAF	recurrence of atrial fibrillation
RLA	left atrial diameter measured from a right parasternal view
QT <sub>c</sub>	QT interval with Fridericia's correction method
ROI	region of interest
SC	peak circumferential strain
SD	standard deviation
SL	peak longitudinal strain
S <sub>m</sub>	peak radial wall motion velocity during systole
SR	peak radial strain
STI	synchronicity time index
TDI	tissue Doppler imaging
t-MVO	time to mitral valve opening
T-PMVT	torsade-like polymorphic ventricular tachycardia
TVEC	transvenous electrical cardioversion
U <sub>high/mid/low</sub>	unipolar surface recording with electrode positioned high, mid or low
VLADD	very long-chain acyl-CoA dehydrogenase deficiency
VPD	ventricular premature depolarization
VT	ventricular tachycardia

# PREFACE



Equine electrocardiography (ECG) is still poorly developed when compared to electrocardiography in human and small animal medicine. Until now, the clinical use of ECG in horses is restricted to surface ECG recordings for diagnosis of rate and rhythm disturbances. Limited attention is given to electrode position and different lead recordings. Apart from a series of studies on vectorcardiography and the clinical significance of changes in T waves fifty years ago, hardly any research was dedicated to the potential of electrocardiography in horses. Nowadays, with affordable wireless ECG units available to the equine clinician, dysrhythmias appear more common than expected. As a result, more questions emerge regarding normal values, diagnosis and mechanisms of cardiac dysrhythmias, driving research into the field of equine dysrhythmias and electrocardiography.

In the introduction of this thesis, a brief overview is given of the extensive knowledge regarding cardiac electrograms in human and small animal medicine. In a second part, a summary is provided regarding standard ECG recording in horses with emphasis on the recording technique and the interpretation of the surface ECG.

The research part of the thesis is divided in two sections. In the first section the clinical importance of surface ECG recordings was studied in two diseases that are known to affect the heart. The second section describes new recording techniques which have specific advantages to investigate the atrial electrical activity of the equine heart.



# GENERAL INTRODUCTION



## ELECTRICAL PROPERTIES OF THE HEART

Throughout history, horses have been admired for their extraordinary athletic ability. Decades of selective breeding have further contributed to the extraordinary cardiovascular capacity of horses. The central and most important organ in maintaining this cardiovascular capacity is the heart.

Essentially, the heart functions as a pump. With each contraction, deoxygenated blood transported from the body to the right side of the heart is pumped to the lungs for oxygenation; oxygenated blood returning to the left side of the heart is subsequently distributed throughout the body. In order for this pump function to be effective, the cardiac contraction needs to be completed in an orderly fashion, where first the two atria contract, followed by contraction of both ventricles. Contraction of cardiac myocytes occurs only in response to an action potential. The electrical impulse starts in the sino-atrial (SA) node, located in the right atrium, and spreads sequentially to the left atrium, through the atrioventricular (AV) node, over the Bundle of His, the left and right bundle branches and the terminal fibers of the widely spread Purkinje system to the equine ventricular myocardium.<sup>1,2</sup>

Upon appropriate stimulation, tiny pores and channels in the cardiac cells open and close in a predefined way to allow specific ions to move across the cell membrane. This movement of ions results in changes in the transmembrane potential and generation of an action potential.<sup>3</sup> Each time an action potential is generated, myocardial cells go through a process of depolarization, followed by repolarization and a resting phase. In certain specialized conducting cells, called pacemaker cells, the transmembrane potential does not remain constant in the resting phase, but slowly depolarizes. When this spontaneous depolarization reaches the threshold potential, it generates an action potential by itself, a process called 'automaticity' (Fig. 1).<sup>3,4</sup>

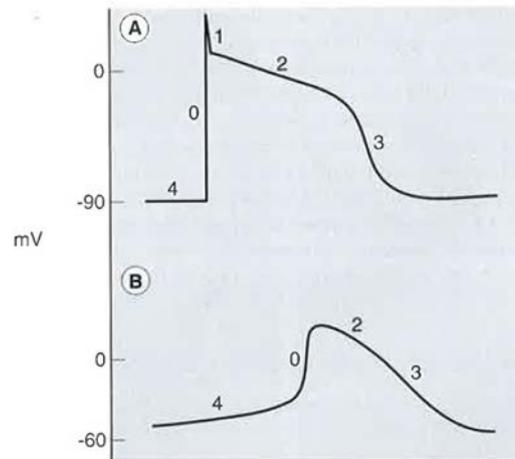


Figure 1: Phases of the cardiac action potential in ventricular myocardial cells (A) and pacemaker cells (B). Phase 0 is the upstroke of the action potential, which is faster in ventricular myocardial cells where it is due to an inward movement of both sodium and calcium. Phase 1 is the rapid repolarization, primarily due to an almost complete inactivation of the inward sodium and calcium current. Phase 2 is the plateau phase of the action potential, which is prominent in ventricular muscle but not in pacemaker cells. It depends on a continued entry of sodium and calcium ions through their major channels and a minor membrane current due to the  $\text{Na}^+\text{-Ca}^{2+}$  exchanger. Phase 3 is the repolarization phase which is due to an outward current of potassium. Phase 4 is the electrical diastolic phase or resting phase of the action potential. In pacemaker cells, changes in the currents of potassium, calcium and the funny current (constituted by sodium and potassium) produce pacemaker activity.<sup>5</sup>

The rate of spontaneous depolarization is fastest in SA nodal cells, but the AV node and Purkinje fibers also have automaticity and will take over as a pacemaker if the SA node fails to depolarize.<sup>5</sup>

During the processes of depolarization and repolarization, the movement of ions causes a current to flow across the cell membrane at various points, and a difference in potential arises between one part of the cell and another. When the current is flowing, an electrical field is set up around the cell, which acts as a dipole. When the cell is depolarized or repolarized and hence in a stable state, no current is flowing across the cell, and no electrical field is formed around it. Each myocyte forms its own electrical field, but the individual fields summate to produce an electrical field around the whole heart, which can be regarded as a single dipole.<sup>3,6</sup> If the changes in the electrical field are large enough, they can be detected on the body surface by electrocardiography (ECG). The electrical field changes associated with SA node depolarization are too small to be

detected on the surface ECG. But when the electrical impulse spreads from the SA node over the atrial myocardium, the generated electrical potentials produce a P wave on the surface ECG. The impulse is then conducted slowly through the AV node and rapidly over the His bundle and bundle branches, producing electrical potentials which are again too small to be recorded on the body surface. This is reflected on the ECG by an isoelectric line, the PR segment. From the Purkinje fibers, the impulse is widely spread from cell to cell throughout the right and left ventricular myocardium, generating the QRS complex on the surface ECG. The repolarization of this large tissue mass is equally visible as the T wave on the ECG (Fig. 2).<sup>7</sup>

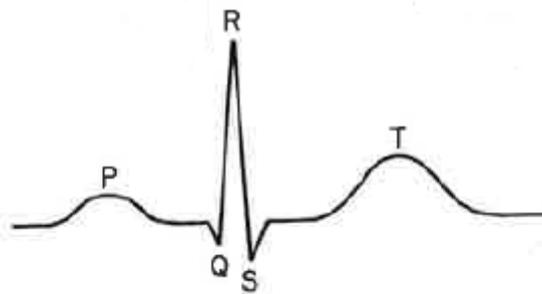


Figure 2: Normal sinus beat with P wave, QRS complex and T wave.

The QRS complex is composed of various components, defined according to international agreements. By convention, the first positive (upward) deflection is an R wave. The first negative (downward) deflection that precedes an R wave is called a Q wave. The first negative deflection that follows an R wave is the S wave. Subsequent positive deflections are R' waves and subsequent negative deflections S' waves. Capital and lower case letters are used to indicate the approximate size of the various deflections. A capital letter represents a deflection of large amplitude, a lower case letter a deflection of low amplitude.<sup>8</sup>

## ELECTROCARDIOGRAPHY IN HUMAN AND VETERINARY MEDICINE

### HUMAN MEDICINE

August D. Waller was the first to record the electrical impulses of the heart from the body surface of animals and man. He used a capillary electrometer: two limbs were dipped into bowls containing salt solution and connected through metal wires to the two poles of the electrometer (Fig. 3). This historical event took place in 1887, and was witnessed by his friend Willem Einthoven.<sup>9</sup>

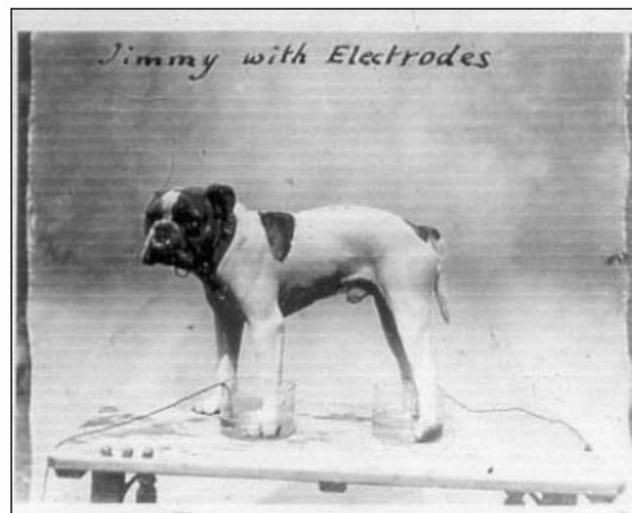


Figure 3: Waller's dog Jimmy, ready for the recording of an electrocardiogram, with his feet in saline.

The term 'electrocardiogram' was first introduced by Waller, but it was Einthoven who developed the string galvanometer, which gave much more accurate tracings of the heart's electrical activity.<sup>10</sup> Today's ECGs are still recorded using galvanometers, but the recording technique has greatly evolved. Where at the beginning of electrocardiography leads to record an ECG were mostly unipolar, soon they were recorded from bipolar leads: a connection between a positive and a negative electrode allowing the recording of the potential difference between them. Recordings are now made from 12 leads in 2 different planes to allow a complete look at the heart and the recording of the time-dependent electrical axis of the heart. The electrical activity generated in all myocytes produces a three-dimensional potential field. The electrical axis refers to the mean

direction of the potentials during the cardiac cycle. The primary clinical significance of the mean electrical axis (MEA) is the diagnosis of left or right axis deviations, which can indicate a conduction abnormality or ventricular enlargement. In the frontal plane, Einthoven's standard bipolar leads I, II and III are recorded using four electrodes. Lead I is recorded between the right arm electrode (-) and the left arm electrode (+), lead II between the right arm electrode (-) and the left foot electrode (+) and lead III between the left arm electrode (-) and the left foot electrode (+). The fourth electrode, which is usually positioned on the right foot, serves as a reference electrode. For the augmented limb leads the positive exploring electrode (right arm for aVR, left arm for aVL and left foot for aVF) is compared to the average of the remaining two electrodes (-) (Fig. 4).

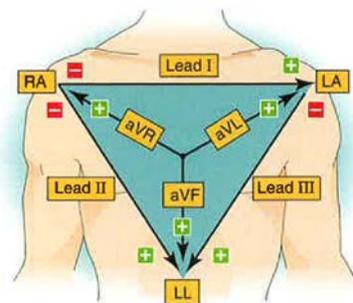


Figure 4: The frontal plane limb leads.<sup>5</sup>

Translating each of these six frontal leads so that they pass through a common point defines a circular coordinate system, used to determine the direction and magnitude of the mean electrical axis of the heart in the frontal plane (Fig. 5).

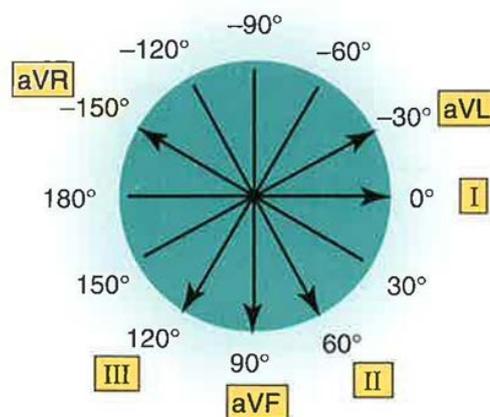


Figure 5: Redrawing of the six limb leads through a common central point.<sup>5</sup>

In the transverse plane, six precordial leads are recorded. These allow to look at the heart from a different angle, and provide additional information on cardiac electrical activity (Fig. 6). The positive connection is one of six different locations on the chest wall, and the negative connection is electrically defined in the middle of the heart by averaging the three limb electrodes.

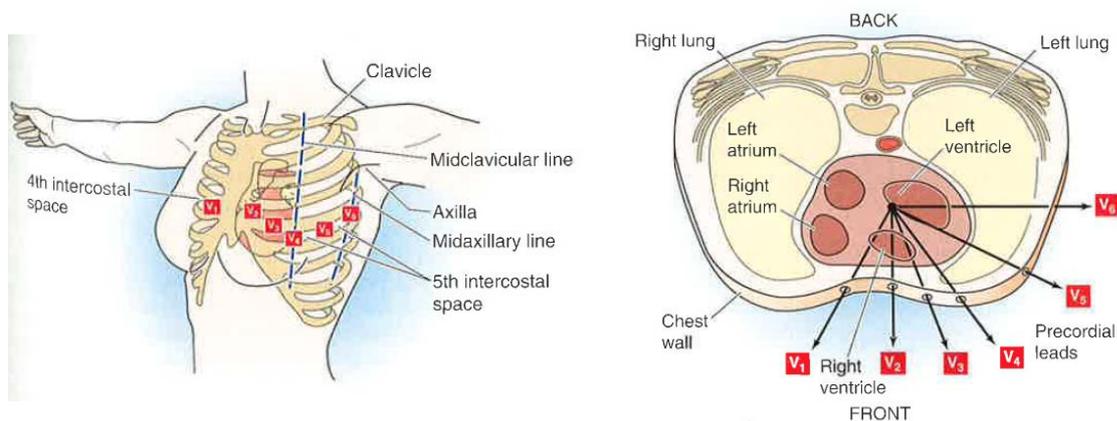


Figure 6: Position of precordial leads in the transverse plane.<sup>5</sup>

Surface ECG is an essential part of a cardiac examination in both man and animals. In its early days, it was used exclusively for determination of rate and rhythm abnormalities. The importance of electrocardiography as a diagnostic tool brought along a continuous development of the technique, with research in human medicine leading the field. As a consequence, electrocardiography in man is no longer restricted to the assessment of rate and rhythm, but can also be used for the diagnosis of structural and electrical cardiac diseases. Examples, which will be briefly discussed below, include cardiac hypertrophy, myocardial infarction, long QT syndrome and Brugada syndrome.

Soon after the advent of clinical electrocardiography it was recognized that characteristic electrocardiographic deviations occur in association with hypertrophy of the cardiac chambers. Over the course of many years, specific electrocardiographic criteria have been established for the diagnosis of ventricular hypertrophy.<sup>11-14</sup> Among those criteria are deviation of the mean electrical axis of the heart and an increased amplitude of the QRS complex. In case of myocardial infarction (MI), the diagnostic value of electrocardiography is well known,<sup>15</sup> and it remains the initial test in identifying both

acute MI and remote MI.<sup>16</sup> Infarcted cardiac tissue loses its electrical characteristics, resulting in an altered depolarization and repolarization pattern. These alterations can be seen on the ECG as ST segment elevation or depression, tall and peaked T waves changes and/or the appearance of pathological Q waves.<sup>16,17</sup> Not only the presence of a MI can be detected, but also the exact localization of the infarcted area.<sup>18</sup> Electrocardiography can also be used for the diagnosis of pericardial or pleural fluid from the decreased voltage on the ECG, but the sensitivity of this diagnostic technique is low (26%).<sup>19</sup>

Jervell and Lange-Nielsen were the first to describe a pronounced prolongation of the QT interval in four children of the same family.<sup>20</sup> Currently, both a congenital hereditary and an acquired form of the long QT syndrome are known as important causes of sudden cardiac death.<sup>21</sup> The syndrome is characterized by an abnormally long cardiac repolarization. The diagnosis of the syndrome is made from inspection of the ECG.<sup>21</sup> More recently, Brugada and Brugada linked a unique ECG pattern to cases of sudden cardiac death.<sup>22</sup> They described apparent right bundle branch block and persistent ST segment elevation in precordial leads V<sub>1</sub>-V<sub>3</sub> in a group of patients suffering from aborted sudden death without demonstrable structural heart disease. Genetic data links the syndrome to an ion channel gene mutation, supporting the hypothesis that the Brugada syndrome is a primary electrical disease resulting in abnormal electrophysiologic activity in right ventricular epicardium.<sup>23</sup> Patients suffering from the Brugada syndrome have a propensity for the development of life-threatening ventricular tachydysrhythmias.<sup>24</sup> Primary diagnosis of the syndrome is made from precordial V<sub>1</sub>-V<sub>3</sub> ECG recordings which show the most prominent changes.<sup>24</sup>

Progress in electrocardiography has not only been made in the diagnosis of different disease states. Research was also directed to the development of new techniques to record the cardiac electrical activity, in an attempt to overcome some of the limitations associated with surface ECG. Due to the distance between the body surface and the heart, the amplitude of electrical signals from different cardiac structures is small or even absent on a surface ECG, complicating the differentiation of supraventricular and ventricular tachydysrhythmias. A first attempt to record electrical activity in closer proximity to the heart were the precordial recordings. These six unipolar leads, recorded in a plane transverse to the plane of the limb leads, offered a look at the heart from a whole new perspective, allowing the diagnosis of otherwise unnoticed

abnormalities,<sup>25</sup> such as the Brugada syndrome. Esophageal electrocardiography was the first technique that allowed the recording of cardiac electrical activity from within the body. The technique facilitates P wave identification by magnifying them.<sup>26</sup> The value of esophageal electrocardiography for diagnosing complex dysrhythmias has been recognized since many years.<sup>26-29</sup> A more recent development is the use of the esophagus to deliver electrical stimuli to atria or ventricles for diagnostic and therapeutic purposes.<sup>30</sup> The technique has proven useful for temporary cardiac pacing in case of bradycardia and for termination of supraventricular tachydysrhythmias such as atrial flutter.<sup>31</sup> Transesophageal pacing has also been used to study the function of sinus node and AV node and to reveal the mechanism of reciprocating supraventricular tachycardia.<sup>32-35</sup>

Although being more invasive, introducing electrodes in the atria or ventricles further improved electrogram recording and allowed selective temporary or permanent cardiac pacing. Additionally, electrical activity from low amplitude cardiac structures could be recorded from intracardiac electrodes. Simultaneous recording from multiple intracardiac electrodes allowed to follow the electrical impulse from sinus node to atria, AV node, His bundle and bundle branches. Over the years, intracardiac recordings have yielded information that has increased the understanding of dysrhythmias.<sup>36</sup> In electrophysiologic studies the cardiac mapping technique is used to identify the origin of ectopic foci or to diagnose specific dysrhythmias, such as the pre-excitation syndromes. In these syndromes, an accessory pathway communicates between the atria and the ventricles, besides the AV node. Because this accessory pathway does not share the conduction-slowness properties of the AV node, the ventricles can become depolarized too early, potentially leading to an atrioventricular reentrant tachycardia.<sup>37</sup> A well-known example is the Wolff-Parkinson-White syndrome, in which the bundle of Kent forms an extra connection between left atrium and left ventricle (type A) or right atrium and right ventricle (type B).<sup>38</sup> The intracardiac electrodes were subsequently used to ablate the accessory path or ectopic focus in order to terminate tachydysrhythmias such as pre-excitation, atrial fibrillation or ventricular tachycardia.<sup>39,40</sup>

## SMALL ANIMAL MEDICINE

Similarity between the human and small animal conduction system and the fact that small animals have been used as an experimental model has resulted in an extended knowledge in the field of canine and feline electrocardiography. Standard ECG recording in cats and dogs is commonly performed in right lateral recumbency and consists of six leads: three bipolar limb leads and three augmented unipolar limb leads (Fig. 7).<sup>8,41</sup>

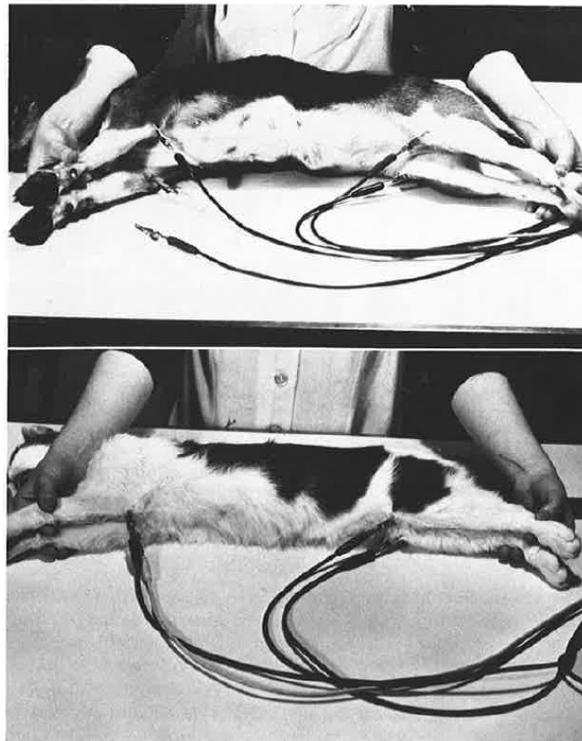


Figure 7: Standard ECG recording in dogs (top) and cats (bottom) using four electrodes, with the animal in right lateral recumbency.

Electrocardiography in cats and dogs is not only used for diagnosing cardiac dysrhythmias, but also provides information about the status of the myocardium. An increase in P wave amplitude can be a sign of right atrial enlargement. The term 'P pulmonale' is used to indicate this ECG feature, since respiratory diseases, and especially collapsed trachea, are often associated with it.<sup>42</sup> However, it can also be caused by cardiac abnormalities, for example tricuspid valve disorders. An increase in P wave duration, indicated with the term 'P mitrale', can reveal left atrial enlargement,<sup>43</sup> as in mitral valve disease.<sup>8</sup> When both changes in P wave are present, biatrial enlargement is suspected.<sup>44</sup> Enlargement of one or both ventricles is associated with changes in the QRS

complex and deviation of the mean electrical axis. Right ventricular enlargement produces large S waves in leads I, II and aVF, with an abnormal right axis deviation.<sup>8</sup> These ECG signs can be associated with conditions such as pulmonary valve disease and heartworm disease.<sup>45,46</sup> Left ventricular enlargement results in tall R waves in leads II, III and aVF, a wide QRS complex and left axis deviation, although not all features have to be present.<sup>8</sup> It can be a sign of for example aortic valve disease, ventricular septum defect or dilated cardiomyopathy.<sup>47,48</sup>

ST segment elevation indicates myocardial infarction, pericarditis or myocardial hypoxia. ST depression suggests myocardial ischemia, acute myocardial infarction, potassium disturbances, digitalis intoxication or trauma to the heart.<sup>8</sup>

QT prolongation can occur in case of electrolyte disturbances, intoxications, hypothermia or central nervous system disorders. A shortened QT interval is seen in hypercalcemia, hyperkalemia or digitalis intoxication.<sup>8,49,50</sup>

Changes in T wave can be clinically significant, but comparison should always be made with previous tracings from the same animal. Increase in amplitude and/or change in polarity can be a sign of myocardial hypoxia, conduction defects, electrolyte imbalances, certain metabolic diseases or drug toxicity.<sup>49,51,52</sup>

Intraventricular conduction abnormalities also lead to characteristic electrocardiographic changes. A bundle branch block leads to a wide and bizarre QRS complex, with a positive QRS complex in leads I, II, III and aVF in case of left bundle branch block and large and wide S waves in lead I, II, III and aVF in case of right bundle branch block.<sup>8</sup>

In small animals esophageal electrocardiography has also been described as a technique to magnify P wave amplitude and hence eases the diagnosis of certain dysrhythmias.<sup>8</sup> The technique is not routinely used in clinical practice. However, esophageal electrodes can also be used for temporary cardiac pacing under general anesthesia. Currently, only transesophageal atrial pacing has been achieved, ventricular capture has not been described yet.<sup>53,54</sup> In contrast to man where there is a close relationship between the heart and the esophagus, the esophagus in dogs is relative distant from the heart.

The technique of intracardiac electrocardiography is well described in dogs, since dogs have often been used in human medicine as a model to study intracardiac recordings.<sup>55</sup> Indications for its use are the same as for human medicine, but the technique is not routinely used in clinical practice.

## EQUINE MEDICINE

The first equine electrocardiogram was published in 1910 by Ellenberger and Scheunert, and was recorded with a string galvanometer in Einthoven's laboratory.<sup>56</sup> Despite the continuous evolution of ECG diagnosis and therapy in human medicine, little progression was made in equine electrocardiography. Up to now, ECG in horses has mostly been restricted to the diagnosis of rate and a number of rhythm disturbances.

This is due to the difference in conduction system in the equine heart: the Purkinje fibers are not limited to the subendocardial myocardium, but extend throughout the myocardium.<sup>1</sup> During the earliest phase of ventricular activation the septal myocardium begins to depolarize generating a variable vector often orientated ventrally and slightly to the right. During the next phase of ventricular activation the apical and middle thirds of the septum are excited simultaneously with the bulk of both ventricular walls. As such, ventricular activation takes place from multiple sites, leading to cancellation of many vectors of local electrical activity. The final phase of activation is responsible for most of the QRS complex seen on the surface ECG and results from the spread of the impulse dorsally during excitation of the basilar third of the septum. Therefore, only the basal part of the septum and a small portion of the left ventricular free wall contribute to the electrical activity seen at the body surface.<sup>1,57</sup>

Thus, in horses, ECGs provide little or no information about heart size. This finding seems to have discouraged the further exploration of electrocardiographic possibilities in horses. In 1957, Brooijmans described the occurrence of changes in T wave morphology as being clinically significant.<sup>56</sup> In the following years, some more work was published on changes in T waves and their relation to poor athletic performance.<sup>58-65</sup> However, later it became clear that T wave changes were a common finding in horses in training which had a normal performance record.<sup>66</sup> T wave changes such as an increase in T wave amplitude or change in polarity are now considered to be non-specific and not helpful in the diagnosis of cardiac disease or poor performance.<sup>1</sup> In 1967, Holmes and Alps published some work on vectorcardiography, in analogy to the construction of the mean electrical axis in human medicine. The main conclusions from these studies were that QRS vectors in normal horses have a wide distribution, and that in horses with cardiovascular disorders no clear axis deviation is present. Hardly any research into the field of electrocardiography has been conducted since then. The entire field of equine

cardiology almost came to a standstill. It was only with the development of echocardiography and the Doppler technique around 1990 that equine cardiology got a new boost. With the upcoming of echocardiography, electrocardiography got further pushed to the background. It wasn't until the very recent development of specific veterinary ECG recording devices that equine electrocardiography regained interest. Recent studies suggest that not all echocardiographic findings are clinically relevant. On the other hand, there is increasing awareness that cardiac rhythm disorders occur more than previously thought.

There is no universal method for recording an ECG in horses. Already in 1954, Brooijmans underlined the importance of using standardized lead positions in clinical diagnostics.<sup>56</sup> However, up to date there is no universal lead system and each clinician seems to have his or her own recording technique. The importance of electrode position is often not recognized leading to non-standardized ECG recordings. As such, it is our experience that subtle ECG changes might be disregarded (Fig. 8). Poor diagnostic criteria further lead to interpretation difficulties and the many confusions existing in the field of equine cardiology.

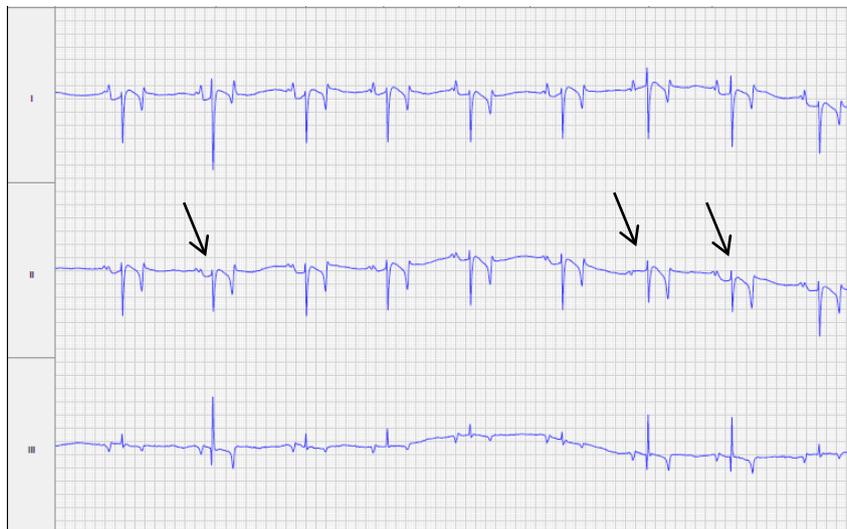


Figure 8: ECG recording demonstrating the advantage of multiple lead recording. When only recording lead II, the presence of three ventricular premature depolarisations (VPDs) (black arrows) could easily be missed because of the subtle changes in QRS morphology and because of the timing of the VPDs, which coincides with the occurrence of the normal QRS complexes, leading to fusion beats. However, when recording additional leads, the three VPDs are easily diagnosed from lead I and especially lead III, which record the cardiac electrical activity from a different angle.

In the next chapter, a summary is provided regarding the current knowledge on ECG recording techniques and interpretation in horses. First, electrode positions to obtain more standardized ECG recordings are provided for different recording modalities. The importance of electrode placement along the MEA of the heart is pointed out and the advantage of multiple lead recordings is stressed. Multiple lead recordings often allow a more accurate identification of dysrhythmias (Fig. 8). Suggestions are made to reduce movement artefacts and to prevent electrode dislodging during exercise. In a second part, diagnostic criteria for the most common rate and rhythm disturbances are given. In addition, examples of common pitfalls in ECG interpretation are shown.

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# CHAPTER 1.1

## AN OVERVIEW OF ELECTROCARDIOGRAPHIC RECORDING TECHNIQUES IN HORSES



# AN OVERVIEW OF ELECTROCARDIOGRAPHIC RECORDING TECHNIQUES IN THE HORSE

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## INTRODUCTION

A cardiac exam always starts with a detailed history and a thorough clinical exam. An imperative aspect of the clinical examination is a skillfully performed auscultation which allows the gathering of important information about cardiac cycle and blood flow.<sup>1</sup> Further diagnostic tests, such as biochemistry, echocardiography and electrocardiography, can then be carried out to obtain additional information about the exact cause and importance of cardiac disease.

Echocardiography allows the imaging of cardiac structures, the determination of chamber size and provides information about cardiac function.<sup>1</sup>

Electrocardiography is the ultimate tool for the diagnosis and classification of dysrhythmias. An electrocardiogram (ECG) can be recorded for brief (ambulatory) or prolonged (e.g. 24-hour or “Holter” recording) periods, at rest and during exercise. ECG recording during exercise used to be reserved to specialized centers because of the expensive equipment. Over the last years, relatively cheap, battery-powered recorders have become available to the equine practitioner for ECG recording under field conditions. In order to correctly diagnose a dysrhythmia, a good quality recording and a thorough knowledge of ECG interpretation are mandatory.

## NORMAL EQUINE ECG

The normal conduction process follows a rather fixed pathway through the heart: from sinus node through the atrial myocardium, the AV node, the Hiss and Purkinje system to the ventricles. As the rhythm originates from the sinus node it is called ‘sinus rhythm’.

Deflections on the ECG originate from the depolarization or repolarization of a relatively large muscle mass, such as the atrial and ventricular myocardium. The depolarization of a small group of cells, such as sinus node and atrioventricular (AV) node, fails to produce sufficient changes in the electrical field. For this reason, the impulse generation in the sinus node is not visible on the ECG.<sup>1</sup>

When the impulse spreads through the atria, the ECG shows a P wave (Fig. 1).



Figure 1: Normal sinus rhythm with P wave, QRS complex and T wave; arrow indicates  $T_a$  wave. Line bar indicates 1 second.

The morphology of P waves is variable: it can be bifid, simple positive or biphasic. When heart rate changes, P wave morphology often changes as well, and even successive P waves are not always identical in the normal horse. At a slow heart rate, the P wave is often bifid. The first peak represents the depolarization of the right atrium and the second one that of the left atrium. In its biphasic morphology, the P wave is usually of the negative/positive type. A normal P wave should take less than 0.16 seconds (Table 1).<sup>2</sup> The  $T_a$  wave, which is the atrial repolarization, is not always clearly identifiable (Fig. 1).

Table 1: Duration of different waves and complexes on a normal ECG.<sup>1-5</sup>

Wave or complex	Duration (sec)
P wave	$\leq 0.16$
PR interval	$\leq 0.5$ (pony: $\leq 0.24$ ) (foal: 0.11 – 0.18)
QRS complex	$\leq 0.14$ (foal: 0.05 – 0.08)
QT interval	$\leq 0.58$ (foal: 0.19 – 0.36)

Atria and ventricles are isolated from each other by fibrous tissue, except at the level of the AV node. The conduction of the impulse through the AV node is very slow, and profoundly affected by vagal tone.<sup>1</sup> As the conduction itself does not result in a

deflection on the ECG, it presents as the flat PR segment. In horses, the normal PR interval may last up to 0.5 seconds, because of their high vagal tone (Table 1).<sup>2</sup>

Once through the AV node, the impulse spreads very rapidly through the His bundle and Purkinje system to depolarize the ventricular myocardium. The latter produces a large deflection on the ECG, the QRS complex (Fig. 1). The QRS complex is composed of various components, defined according to international agreements. By convention, the first positive (upward) deflection is an R wave. The first negative (downward) deflection that precedes an R wave is called a Q wave. The first negative deflection that follows an R wave is the S wave. Subsequent positive deflections are R' waves and subsequent negative deflections S' waves.<sup>6</sup> This means that although the complex is named 'QRS', it has not always – and usually not – a 'QRS' morphology in horses. The rS or rSr' morphology is most common in horses. The duration of the QRS complex should not exceed 0.14 seconds (Table 1).<sup>2</sup>

Each depolarization is followed by a repolarization, represented by the T wave (Fig. 1). In horses, the T wave is very variable in size and orientation and particularly dependent on the heart rate. Even beat-to-beat changes in the RR interval often affect the morphology of the T wave. T waves are not helpful in the diagnosis of cardiac disease<sup>1</sup> but may be helpful to differentiate between a normal and abnormal ventricular beat, and between artefacts (which do not have T waves). The QT interval in normal horses takes no longer than 0.58 seconds (Table 1).<sup>2</sup>

It is essential to realize that the Purkinje fibre system is much more extended in horses than in humans and small animals. Therefore, the equine QRS complex provides little or no information about heart size or the exact origin of an ectopic beat. Basically, it only provides information regarding the heart rate and rhythm.

## EQUIPMENT

The basic equipment consists of electrodes, a recording device and a way to display the trace.

In the past, crocodile clamps were pinched to the horse's skin after application of contact gel or alcohol.<sup>5</sup> Drawbacks of using those electrodes were the fact that they could be painful or result in skin reaction, and that they easily produce artefacts. Self-adhesive electrodes are better tolerated and significantly improve recording quality.

Specific equine self-adhesive electrodes should be used as they contain more gel to improve skin contact and stronger glue to remain in place, even during exercise. Clipping of the hair coat is generally not necessary and even undesirable since it causes the electrodes to fall off more easily, especially during sweating. Extra gel can be used when the hair coat is very long, e.g. during winter, or extra glue in case of excessive sweating.

Any ECG device can be used for ambulatory recording. However, a small, battery-powered device, fixed to the horse's back, allows to make recordings during exercise. The signal can then be digitally stored or wirelessly transmitted (telemetry) through radiofrequency or Bluetooth. Telemetry allows for beat-to-beat real-time monitoring and thus represents an advantage above other systems.<sup>7</sup> When a device has sufficient storage capacity, e.g. on a digital card, also long-term (e.g. 24-hour) monitoring becomes possible.

Nowadays, the recorded signals can be imported into computer software for the automatic analysis of normal and abnormal rhythms. The software detects R waves and screens for sudden irregularities in RR interval. Complex algorithms for the analysis of QRS morphology exist in more advanced software packages designed for human or small animal cardiology. However, these algorithms usually fail to interpret the horse's ECG correctly, partly because of the large T wave on the equine ECG. Therefore, the visual screening of the horse's ECG usually remains necessary.

## RECORDING OF AN ECG

An ambulatory ECG has high diagnostic value for dysrhythmias that are continuously present. For occasionally occurring dysrhythmias, 24-hour monitoring is necessary.<sup>7</sup> This type of monitoring allows the frequency of dysrhythmias to be catalogued. Also when a horse is examined for seizures or collapse, continuous ECG monitoring may be necessary to confirm or rule out a cardiac cause. Many dysrhythmias only occur during exercise while others, although present at rest, may disappear during exercise. Therefore, exercise ECGs are a mainstay in the diagnosis of dysrhythmias and the work-up of a poor performing horse.<sup>8,9</sup>

To start recording an ECG, electrodes need to be attached to the horse's body and connected to the recording device. Different devices may have 3, 4, or up to 10 electrodes (Fig. 2).



Figure 2: Recording device (Televet 100®) with 4 electrode cables (green, yellow, red and black) and a self-adhesive electrode.

There is no universally accepted lead system for the use in large animals.<sup>10</sup> Usually, a single-lead recording is considered sufficient.<sup>11</sup> However, the advantage of a multiple lead system is that each lead detects the potential difference between its 2 electrodes from a unique angle, which might help to differentiate between a normal or abnormal complex (Fig. 3).<sup>12</sup> In addition, when one electrode falls off in a multiple-lead system, the recording can still continue from the remaining electrodes. Whichever method is used, the procedure should be standardized so that ECGs can be compared.<sup>11</sup>

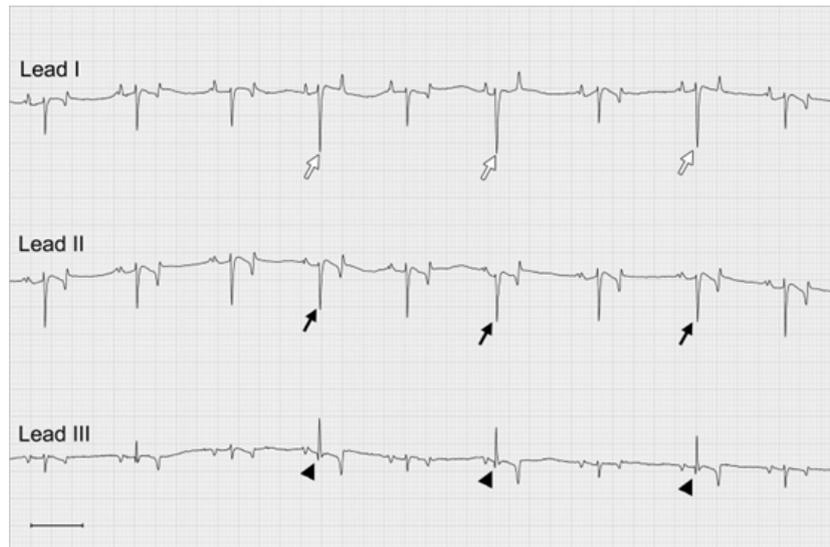


Figure 3: Multiple lead recording from a horse with abnormal QRS-complexes (due to fusion beats) clearly visible in lead III (arrowheads), but easily overlooked in lead II (black arrows). Lead I shows QRS complexes with a larger amplitude (open arrows). Line bar indicates 1 second.

Systems with 4 electrodes are most commonly used. In such a system, the black electrode serves as a reference electrode for the electrocardiograph and can be positioned anywhere on the body surface of the horse. The remaining 3 electrodes are used to construct 3 leads: lead I between the red (right arm, -) and the yellow (left arm, +) electrode, lead II between the red (-) and the green (left foot, +) electrode, and lead III between the yellow (-) and the green (+) electrode.<sup>5</sup> Modern devices will automatically record from all 3 leads at the same time, offering the advantages of a multiple-lead recording. Older devices might require a manual switch between each lead.

The positioning of the electrodes is not strictly defined in horses and can be adapted according to the circumstances. As a general rule of thumb, electrodes need to be positioned along the MEA, which is an average of the cardiac vector and is directed from the apex of the heart towards the base and slightly to cranial and to the right. This means that one electrode should be on the lower thorax near the cardiac apex: between the elbow and xiphoid area. The second electrode should be positioned towards the cardiac base which is more dorsal, in the region between the lower neck and the withers.

Below, some examples for electrode placement are given.

## AMBULATORY ECG RECORDING

For ambulatory recordings at rest, the base-apex lead system gives the best results. It corresponds best with the MEA direction and hence results in the largest deflections for both atrial and ventricular waveforms.<sup>13</sup> The negative (red) electrode is positioned in the lower third of the right jugular groove or on the scapula, corresponding to the base area of the heart. The positive (green) electrode is positioned over the apex beat area of the heart, on the thorax, caudal to the left elbow. The yellow electrode can be positioned on the middle of the left scapula. The remaining black electrode can be positioned anywhere on the body surface of the horse.

## EXERCISE ECG RECORDING

The base-apex system is unsuited for recordings during exercise,<sup>13</sup> since electrodes are then more prone to creating movement artefacts and falling off and can interfere with the freedom of movement of horse and rider. For ridden exercise recordings, an adaptation of the base-apex system should be used.

The negative (red) electrode is placed on the left shoulder blade, near the withers. When saddled, this position is just in front of the left saddle flap. The positive (green) electrode is placed behind the saddle girth on the left, on a position where the leg of the rider does not interfere with it. The remaining yellow electrode can be placed just above or underneath the green one, creating an extra lead. A good position for the reference electrode is just underneath the red one. In this construction, the rider can easily reattach any electrode, and the electrodes are unlikely to be affected by the saddle or girth slipping backwards during fast exercise.<sup>13</sup> The left-to-right component of the MEA is missing here, but the deflections on the ECG are still clearly visible, although the atrial deflection (P wave) will be slightly lower in amplitude.<sup>13</sup> The negative (red) and reference (black) electrodes can also be placed underneath the left saddle flap, which offers extra protection from dislodging.

To prevent electrodes from dislodging, e.g. during intensive exercise or during lunging exercise, one can use an elastic girth around the horse's thorax and place the electrodes underneath the girth. In this vertical modification of the base-apex system, the cranio-caudal orientation of the MEA is lost. Therefore, the P wave will be lower in amplitude

than that of a true base-apex configuration but large QRS deflections will still be present. The negative (red) electrode is positioned on the right side of the withers, and the positive (green) electrode behind the left elbow joint, on the apex beat area. The remaining (yellow) electrode is placed about 10 cm above the green one. The reference electrode can be positioned anywhere under the girth (Fig. 4). The girth can be used during lunging exercise but also during ridden exercise or in trotters, where it is placed just cranial and partially underneath the saddle or harness.



Figure 4: Positioning of electrodes for 24h ECG monitoring or lunging exercise, using a custom designed girth (Orthohorse® Mainat Vet). 'Right arm' corresponds to the red electrode, 'left arm' to the yellow electrode and 'left foot' to the green electrode.

## LONG-TERM ECG RECORDING

For long-term recordings, e.g. 24 hours or more, the recording device, electrodes and wires need to be protected. The girth, with the electrode configuration mentioned above, is suited as it covers all electrodes and wires so that the horse cannot damage these. The recorder itself is placed in a protective box so that it does not get damaged during rolling.

As stated before, no universally accepted lead system exists for recordings in large animals. Adaptations to the systems described above can be made according to personal experience and preferences.

## CONCLUSION

Electrocardiography is the ultimate diagnostic tool when cardiac dysrhythmias are suspected. Nowadays, relatively cheap equipment (1000-3000 €) has become available to the equine practitioner. An ECG can be recorded ambulatory, for a brief period, or for a longer period when monitoring for less frequent dysrhythmias. An exercise ECG is mandatory to assess the importance of certain dysrhythmias found at rest and especially in horses with poor performance.

For the recording of an ECG, self-adhesive electrodes are most appropriate. Modern recording devices offer the possibility of wireless transmission and storing of the recorded signal, allowing online monitoring during exercise and making 24-hour recordings. When the signal can be displayed on a computer, software may aid to analyze the recorded trace. However, visual inspection of the equine ECG usually remains necessary because the large equine T wave may interfere with automatic analysis.

The exact position of the electrodes is currently considered not that important, as long as the leads are constructed along the MEA. However, from our own experience we have found that a standardized approach to ECG recording leads to a more accurate diagnosis of abnormalities. Multiple lead systems have the advantage of being more sensitive and always have one or more “backup” leads in case of electrode dislodgement.

Interpretation of the recorded ECG can be challenging and requires experience. A guideline to the interpretation of an ECG and identification of the different kinds of dysrhythmias will be presented in chapter 1.2.

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## CHAPTER 1.2

# AN OVERVIEW OF ELECTROCARDIOGRAPHIC INTERPRETATION IN THE HORSE



# AN OVERVIEW OF ELECTROCARDIOGRAPHIC INTERPRETATION IN THE HORSE

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## INTRODUCTION

Due to their high vagal tone, horses have a higher incidence of cardiac dysrhythmias at rest than any other domestic species.<sup>1,2</sup> These physiological dysrhythmias are usually abolished when vagal tone decreases and sympathetic tone increases, such as during exercise or excitement.<sup>3</sup> On the other hand, exercise may exacerbate certain dysrhythmias making the recording of an exercise ECG an indispensable part of a cardiac diagnostic work-up.

In this chapter a schematic approach for ECG interpretation is presented and the typical characteristics of common dysrhythmias are described. Finally, common pitfalls are discussed.

## STANDARD APPROACH TO ECG INTERPRETATION

Before all, one should assess quality of the recording and sufficiency for accurate diagnosis. Overinterpretation of artefacts from a poor quality recording is a commonly made mistake.

In order to avoid errors, evaluation of the ECG recording should be performed in a methodical manner.<sup>4</sup> Heart rate, heart rhythm, correlation between P waves and QRS complexes, morphology of P waves and QRS complexes and the duration of the different complexes and intervals should be evaluated.

At rest, the horse's heart rate ranges between 24 and 50 beats per minute (bpm),<sup>5,6</sup> increasing to a maximum of 220-240 bpm during exercise. Heart rates below 24 bpm are called bradycardia, those above 50 bpm tachycardia.<sup>6</sup> Computer software facilitates calculation of beat-to-beat intervals. However, depending on heart rate and electrode position, the tall T wave of the equine ECG is commonly mistaken for a QRS complex by the commercial software. For this reason, manual inspection of the analysis remains compulsory.

Heart rhythm is assessed to determine whether it is regular or irregular although small deviations in RR interval are physiologic. It has been suggested that RR variations of more than 8-20% should be considered as abnormal.<sup>7</sup> This threshold for dysrhythmia detection can be preset in computer software. When the threshold is set low, sensitivity for true irregularities is high, but many physiological RR variations will also be

indicated. If irregularities are present, their nature should be investigated: are they intermittent or persistent, do they occur at random or follow a possibly predictable pattern, are they induced or terminated by any form of excitement?<sup>4</sup>

The final step is to assess morphology and duration of the different waves, and the relation between waves. Each complex should have the same morphology. Each P wave should be followed by a QRS complex and each QRS complex should be preceded by a P wave. On the ECG, premature waves are usually indicated by an apostrophe ('), e.g. P' for indicating the P wave of an atrial premature complex, and QRS' for indicating a ventricular premature complex.

## CLASSIFICATION OF DYSRHYTHMIAS

Dysrhythmias can be classified according to their origin in sinoatrial nodal (SA nodal), atrial myocardial, atrioventricular nodal (AV nodal) or ventricular myocardial dysrhythmias.

### SA NODAL DYSRHYTHMIAS

The SA node, as the natural pacemaker of the heart, can fire too slowly, too fast or at irregular intervals, leading to SA nodal dysrhythmias.

#### Sinus bradycardia

Sinus bradycardia is a rare condition that is usually associated with a physiological high vagal tone, although it can also be pathologic in nature. In those cases sinus bradycardia may lead to poor performance. The distinction between physiological or pathological sinus bradycardia is made by recording an exercise ECG. When caused by high vagal tone, it is abolished by exercise, whereas in pathological bradycardia the chronotropic response is attenuated.<sup>2</sup>

Sinus bradycardia is diagnosed when RR intervals are regular but heart rate is below 24 bpm. All waves and complexes have a normal appearance and the relation between P waves and QRS complexes is normal (Fig. 1). However, other vagally-induced dysrhythmias, such as sinus arrhythmia and 2<sup>nd</sup> degree AV block, may be present concurrently.



Figure 1: Sinus bradycardia. Heart rate is below 24 bpm but every P wave is followed by a QRS complex and every QRS complex is preceded by a P wave. Line bar indicates 1 second.

## Sinus tachycardia

Sinus tachycardia is caused by an increase in sympathetic tone or a decrease in parasympathetic tone and can be a physiological response in order to increase cardiac output. When it is seen at rest, the animal might have an increased sympathetic tone, caused by e.g. fever, hemorrhage, anemia, shock or heart failure.<sup>6</sup>

Sinus tachycardia is characterized by a resting heart rate above 50 bpm, with regular RR intervals. The morphology, duration and relation of P waves and QRS complexes is normal (Fig. 2). At higher rates, P waves may be masked by the preceding T wave.

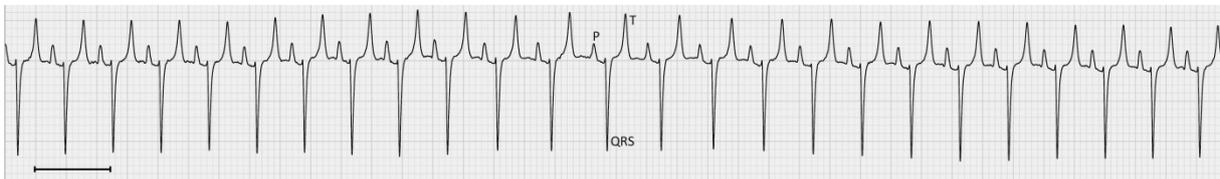


Figure 2: Sinus tachycardia. Heart rate is above 50 bpm but every P wave is followed by a QRS complex and every QRS complex is preceded by a P wave. Line bar indicates 1 second.

## Sinus arrhythmia

Sinus arrhythmia is a periodic waxing and waning of heart rate, caused by alterations in vagal tone.<sup>6,8</sup> It can occur in resting horses but appears a lot more frequently during the recovery period following exercise. Usually, the rhythm becomes regular again when heart rate slows further to resting level. The condition is considered physiological but should disappear with a decreasing parasympathetic or increasing sympathetic tone, e.g. during exercise.<sup>4</sup>

On an ECG, sinus arrhythmia is characterised by varying PP and RR intervals. P-QRS relations are normal and QRS complexes always have a normal morphology, but the shape of the P wave can be variable (Fig. 3).<sup>8,9</sup> Heart rate can be normal, but is usually between 50 and 110 bpm. Sometimes sinus arrhythmia can have a more or less cyclic pattern, starting with a long RR interval, followed by a number of shortening RR intervals, until a long RR appears again.

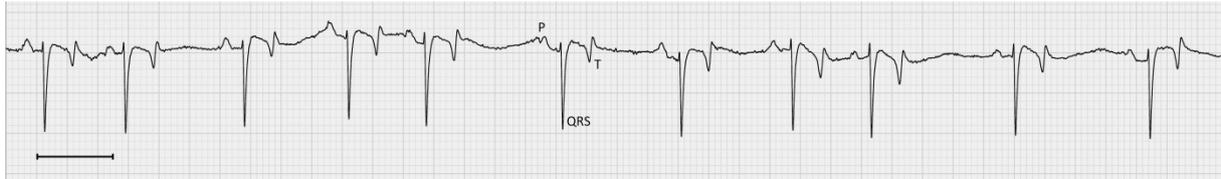


Figure 3: Sinus arrhythmia. RR intervals are irregular but every P wave is followed by a QRS complex and every QRS complex is preceded by a P wave. Line bar indicates 1 second.

### Sinus (exit) block and sinus arrest

Sinus block and sinus arrest are characterized by long pauses during which there are no P-QRS-T complexes. High vagal tone is considered to be the underlying cause of these dysrhythmias, preventing the depolarization to exit the sinus node (sinus block) or interrupting the firing rate of the SA node (sinus arrest).<sup>10</sup> They are infrequent and rarely pathological. Similar to sinus arrhythmia, these dysrhythmias are usually vagally induced and should disappear during exercise. In rare cases, cardiac output can drop to such a low level that syncope can develop.

Horses with sinus block and sinus arrest have a slow to normal heart rate. Characteristic on the ECG is that the PP and RR intervals are equal to (sinus block) or greater than (sinus arrest) two normal PP or RR intervals.<sup>6,9</sup> All other aspects of the ECG are normal: the morphology of P waves and QRS complexes is normal, every P wave is followed by a QRS complex and every QRS complex is preceded by a P wave (Fig. 4). During a long pause however, a junctional or ventricular escape beat may occur on the ECG,<sup>9</sup> appearing as QRS complexes with abnormal morphology and duration, and no relation with a P wave (see below).

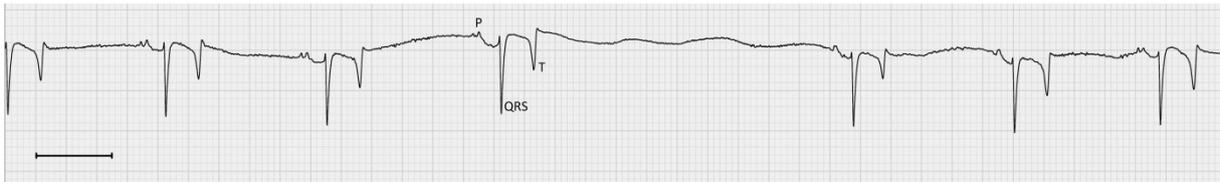


Figure 4: Sinus block. RR interval is equal to 2 normal RR intervals. Line bar indicates 1 second.

## ATRIAL MYOCARDIAL DYSRHYTHMIAS

Atrial myocardial dysrhythmias are caused by abnormal impulse formation from the atrial myocardium outside the SA node.

### Atrial premature depolarization

Atrial premature depolarizations (APDs) or atrial premature beats occur earlier than expected in the normal basic rhythm.<sup>8</sup> In athletic horses APDs occur occasionally, but performance is affected only when they cause an excessive heart rate during exercise or predispose to paroxysmal atrial fibrillation.<sup>11</sup> When, in the absence of systemic disease, APDs occur frequently, e.g. one to five per minute, it is more likely that underlying atrial disease is present.<sup>2</sup>

On the ECG, a premature P' wave is present of which the morphology can be normal or abnormal. Whether or not the P' wave conducts to the ventricles depends on the timing within the cardiac cycle.<sup>12</sup> If conduction occurs, QRS morphology and duration are normal (Fig. 5). The impulse of the APD usually enters the SA node and resets the 'timer' of the node. This resetting interrupts the basic rhythm of the node, causing it to resume its normal pacemaker activity at an earlier time than would have been expected from the normal RR interval. The interval from the premature complex to the next normal QRS complex is called a 'non-compensatory pause', because it is less than a compensatory pause.<sup>13</sup> In some occasions the SA node is not reset by the APD and continues to fire at the expected point in time, but fails to produce a P wave. In this case the length of two RR intervals preceding the APD is equal to the length of the RR intervals between the sinus beat preceding the APD, the APD and the sinus beat following the APD. In rare cases, an interlaced APD appears between 2 normal sinus beats, without interrupting

the basic rhythm of the SA node. No P wave is dropped and an extra P' wave appears between the two normal P waves.



Figure 5: Atrial premature depolarization. The P' wave occurs prematurely and is followed by a normal QRS-T complex. There is a non-compensatory pause which indicates that the SA node is reset. Line bar indicates 1 second.

### Atrial tachycardia

When four or more APDs occur successively, atrial tachycardia is present.<sup>4,12</sup> It can be caused by underlying atrial myocardial disease, but other possible causes include electrolyte disturbances or systemic disease.<sup>12</sup> Atrial tachycardia should be distinguished from sinus tachycardia, which is a normal physiological response. In atrial tachycardia atrial rate is high, without an apparent reason for a high heart rate such as excitement or pain.

On the ECG, P' waves occur at an increased rate, may show a regular or irregular rhythm and have a normal or abnormal morphology. At higher rates, P' waves are buried in the preceding T wave and become invisible. P' waves that conduct to the ventricles result in a QRS complex with normal morphology.

### Atrial fibrillation

Atrial fibrillation (AF) is a condition whereby the atria no longer contract in a coordinated manner, instead, they quiver.<sup>14</sup> It is particularly common in horses because of their large atria and high vagal tone.<sup>4</sup> AF can be paroxysmal, e.g. in Thoroughbreds during racing, and then spontaneously revert to sinus rhythm within 72 hours. Most frequently, however, AF is permanent once it starts, and does not convert spontaneously. At rest, it will usually not result in clinical symptoms, because of the relatively small contribution of the atrial contraction to ventricular filling and cardiac output. During exercise, however, heart rate may become excessively high, whereby the decreased ventricular filling time results in a decreased stroke volume. The absence of

atrial contraction exacerbates this decrease, potentially resulting in poor performance, especially in high demanding sport disciplines such as racing, eventing or endurance.<sup>15</sup> AF is characterized by the absence of P waves, the presence of fibrillation waves or f waves and irregularly irregular RR intervals with normal QRS morphology (Fig. 6).<sup>11</sup> In case of very short RR intervals, the T wave will be opposite to the QRS complex, which might differ from the other T waves. Such a complex should not be mistaken for a ventricular premature beat. The morphology of the f waves varies from coarse to fine, often alternating within recordings. The frequency of the f waves can be as high as 500 per minute, but only a limited number of impulses is conducted through the AV node. In the absence of underlying cardiac disease, ventricular rate at rest is normal. During excitement or exercise, the heart rate easily surpasses the maximal heart rate of 240 bpm, often resulting in short lasting episodes of high ventricular rates up to 250 to 450 bpm.



Figure 6: Atrial fibrillation. P waves are absent, f waves with variable morphology are present, QRS morphology and duration are normal but RR intervals are irregular. Line bar indicates 1 second.

## AV NODAL DYSRHYTHMIAS

The normal AV node 'passes' the atrial impulse to the ventricles. In AV block, this conduction towards the ventricles is delayed (1<sup>st</sup> degree), intermittently blocked (2<sup>nd</sup> degree) or completely absent (3<sup>rd</sup> degree).

### First degree AV block

In 1<sup>st</sup> degree AV block, the conduction of the atrial impulse through the AV node is delayed. In horses, this is usually due to the vagal tone,<sup>8</sup> but it can also be caused by drugs such as  $\alpha_2$ -agonists or digoxin.<sup>4</sup> The dysrhythmia is generally physiological and of little clinical significance. AV nodal disease is present only on rare occasions.

During 1<sup>st</sup> degree AV block, each P wave is followed by a QRS complex and every QRS complex is preceded by a P wave but the PR interval is prolonged (>0.5 sec). The morphology of P waves and QRS complexes is normal.

### Second degree AV block

Intermittent failure of the atrial impulse to conduct toward the ventricles is called 2<sup>nd</sup> degree AV block. This is the commonest physiological dysrhythmia found in horses<sup>10</sup> and is usually caused by a high vagal tone.<sup>3</sup> It is considered to be physiological and could be a normal mechanism in regulating blood pressure.<sup>4</sup> During exercise or excitement, this type of dysrhythmia should disappear with the abolishment of the high vagal tone.

Two types of 2<sup>nd</sup> degree AV block can be distinguished: Mobitz type I (or Wenckebach periodicity) and Mobitz type II. In type I blocks, there is a lengthening of the PR interval on the ECG, until a P wave is not followed by a QRS complex; however, the PR interval immediately preceding the dropped beat is not necessarily the longest one in the sequence. Mobitz type II blocks are characterised by P waves that are periodically not followed by a QRS complex, without preceding sign of the block.<sup>8</sup> In both cases, the morphology of P waves and QRS complexes is normal. Every QRS complex is preceded by a P wave, but not every P wave is followed by a QRS complex (Fig. 7). Of the two types of blocks, Mobitz type II is the most frequently observed.<sup>10</sup>

Sometimes 2<sup>nd</sup> degree AV block can be so profound that it is considered a pathological dysrhythmia, i.e. advanced 2<sup>nd</sup> degree AV block. In those cases, several successive P waves are blocked before a normal conduction takes place. Long pauses may lead to a drop in blood pressure and even syncope. Long term ECG recording may be required in order to diagnose this condition. The ECG shows normal PP intervals but multiple, successive P waves are not followed by a QRS complex. QRS complexes following a P wave have a normal morphology and duration. During long pauses, escape beats may appear.



Figure 7: Second degree AV block, Mobitz type I. PQ interval lengthens until one P wave is not followed by a QRS complex (arrow). PP interval is regular. Line bar indicates 1 second.

### Third degree AV block

In 3<sup>rd</sup> degree AV block or complete heart block, none of the atrial impulses conducts through the AV node. The ventricles are left to contract according to their own intrinsic escape rhythm, which is usually slower than normal sinus rhythm. This condition is invariably pathological and can be caused by degenerative or inflammatory AV nodal disease.<sup>12</sup> It can be associated with syncope or weakness and is only rarely reversible.

The ECG shows P waves with normal morphology and a regular PP interval. P waves have no relationship with the QRS complexes. The rate of the P waves is usually high as a reflex to hypotension.<sup>9</sup> QRS complexes can be bizarrely shaped although a ventricular escape rhythm originating closely to the AV node is usually regular and results in a close to normal QRS complex (Fig. 8).

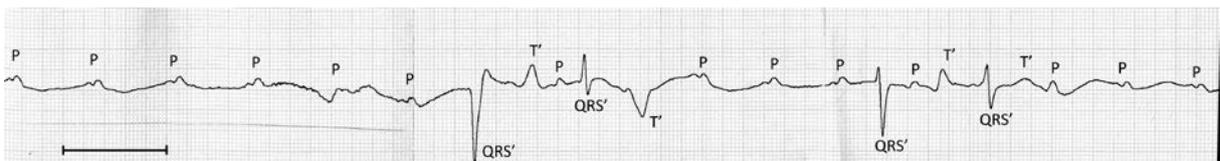


Figure 8: Third degree AV block. PP intervals are regular but P waves have no relationship to QRS complexes. QRS complexes have bizarre shapes. First QRS complex is an example of an escape beat. Line bar indicates 1 second.

## VENTRICULAR DYSRHYTHMIAS

Ventricular dysrhythmias are the consequence of abnormal impulses that arise somewhere in the ventricular myocardium.

## Ventricular premature depolarization

Ventricular premature depolarizations (VPDs) occur earlier than expected during normal sinus rhythm. They are less frequent in horses in comparison with other species,<sup>4</sup> and their significance and underlying etiology is not well understood.<sup>2</sup> However, they can be caused by myocardial or systemic disease and potentially lead to ventricular tachydysrhythmias.<sup>2,10</sup> This is why horses with VPDs at rest should be retired from ridden work and thoroughly examined.<sup>2</sup>

Because the VPD conducts in a different direction and from cell to cell, not over specialized conduction tissue, the resultant QRS' complex is longer in duration and has a different morphology.<sup>8</sup> Depending on the site of origin, the QRS' complex may have a bizarre or close to normal appearance. Multiple lead recordings are therefore helpful to detect certain VPDs. The VPD is not associated with a preceding P wave (Fig. 9).<sup>2</sup> Naturally, a normal P wave with variable PR interval may, by coincidence, precede the VPD, but it is not associated with the VPD. The abnormal QRS complex is usually followed by a compensatory pause, since the first sinus beat after the VPD occurs while the ventricles are still refractory. However, VPDs may occasionally present without disturbing the underlying rhythm, i.e. 'interlaced' beats. On rare occasions, by coincidence, the ventricle may be depolarized by a normally conducted beat and a VPD that occur at the same time. The resultant QRS' is called a 'fusion beat' and has a morphology which is a mixture between the normal QRS and VPD morphology (see chapter 1.1: An overview of electrocardiographic recording techniques in the horse, Fig. 3).

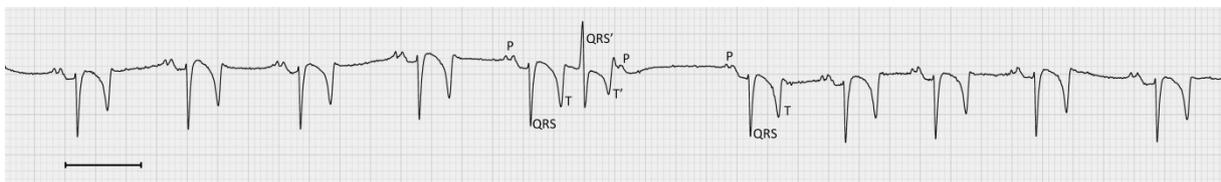


Figure 9: Ventricular premature depolarization. QRS' complex has a bizarre morphology and is not preceded by a P wave. RR' interval is too short. VPD is followed by a compensatory pause. Line bar indicates 1 second.

## Ventricular escape beat

When for some reason the ventricles are not depolarized by an impulse and heart rate becomes too low, a ventricular escape beat arises from the ventricular myocardium. Escape beats occur later than expected in the normal sinus rhythm and can be said to “rescue” the ventricles from asystole. They are a sign of underlying atrial or junctional disease<sup>4</sup> that results in bradycardia.

The ECG shows a longer than normal RR' interval and the QRS' complex has an abnormal morphology and duration (see 1<sup>st</sup> QRS complex on Figure 8).<sup>9</sup> A P wave can be absent, or is non-conducted with no correlation to the QRS' complex. When escape beats arise in close proximity to the AV node, the QRS' complex may have a fairly normal appearance. For this reason, multiple lead recordings may be helpful for diagnosis.

## Ventricular tachycardia

When four or more VPCs occur in a row, this is termed ventricular tachycardia (VT).<sup>2,4</sup> VT may be paroxysmal or sustained if it persists for many minutes or hours.<sup>8</sup> It nearly always indicates underlying cardiac or systemic disease.<sup>4</sup> VT is a potentially life-threatening dysrhythmia since it can lead to ventricular fibrillation and death.<sup>2</sup>

Ventricular tachycardia is characterized by abnormal QRS' complexes which are not related to P waves (Fig. 10). When the QRS' complexes all have the same morphology, monomorphic VT is present. When the ventricular impulses arise from more than one location, the QRS' complexes have different morphologies, which results in polymorphic VT. Sometimes no P waves can be identified because they get hidden in the QRS' complexes. The heart rate is higher than normal but may range from around 50 to more than 200 bpm. The rhythm can be regular, usually when monomorphic VT is present, or irregular. When a premature ventricular complex follows very closely after the T wave of the preceding complex, the 'R-on-T' phenomenon is present. This phenomenon is a potential initiator of a fatal dysrhythmia.<sup>12</sup>



Figure 10: Ventricular tachycardia. Two VPCs (long arrows) are followed by one normal P-QRS-T complex and a train of VPCs: VT (short arrows). Line bar indicates 1 second.

## Ventricular fibrillation

During ventricular fibrillation there are no longer coordinated contractions of the ventricles. It is almost invariably a terminal event despite treatment.

The ECG shows undulations of the baseline with no identifiable QRS complexes or T waves (Fig. 11). P waves can still be present but are no longer followed by QRS complexes.

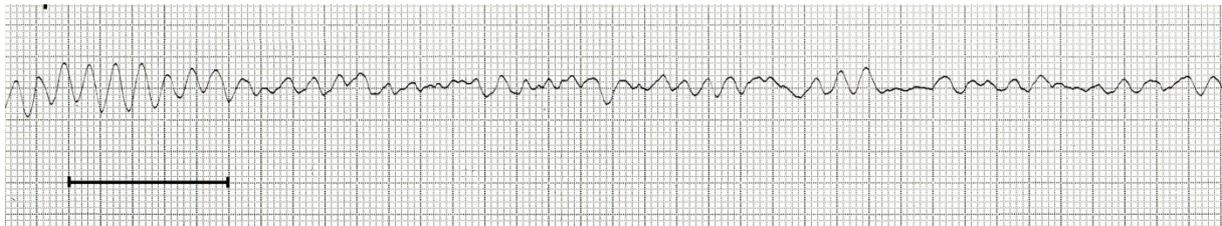


Figure 11: Ventricular fibrillation. Undulating baseline with no identifiable QRS complexes or T waves. Line bar indicates 1 second.

## COMMON PITFALLS

Sometimes artefacts arise on an ECG recording, which can be mistaken for P waves or QRS complexes and thus lead to misinterpretations. Artefacts are deflections on an ECG recording that are not caused by electrical activity of the heart.

The commonest cause of artefacts is movement, either of the horse or of the lead wires or electrodes. It is helpful to use self-adhesive electrodes and to prevent the wires from swinging, but when recording an ECG of an exercising animal, artefacts are almost impossible to avoid. These artefacts are seen as sharp deflections which occur at random but sometimes can resemble a QRS complex. Muscle tremor causes very sharp and

narrow multiple deflections of the baseline (Fig. 12). Large undulations in the baseline usually are due to exaggerated respiratory motion.<sup>4</sup>

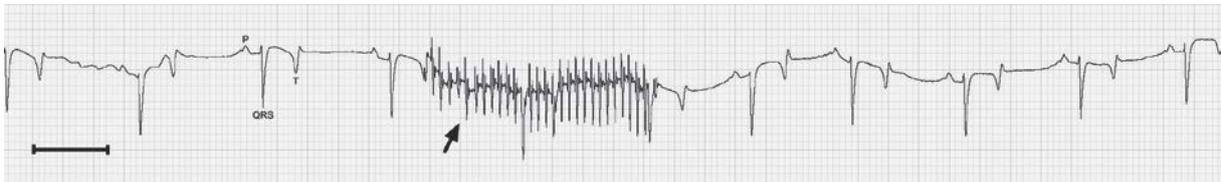


Figure 12: Muscle tremor causing sharp narrow deflections (arrow) of the baseline in the ECG trace. Line bar indicates 1 second.

Another source of artefacts is interference from electrical mains, especially when using recorders that are mains-powered. These artefacts are characterized by sharp, narrow and regular deflections of the entire ECG recording with a frequency of 50 Hz. They should not be mistaken for atrial fibrillation since P waves are still present and the undulations are regular. By using the filter on the ECG recorder, those artefacts can be largely avoided. A simple rule that can help distinguishing true dysrhythmias from artefacts is that artefacts do not have T waves.

Changes occurring on the ECG during exercise can also lead to misinterpretations. P waves can change in amplitude and shape,<sup>8</sup> and often a gradual 'displacement' of the P wave in the direction of the preceding T wave can be seen with increasing heart rate. Eventually, the P wave can disappear entirely in the preceding T wave.

At rest, the T wave can present as a positive, negative or biphasic wave, but during exercise or stress, its polarity becomes opposite to the QRS complex (Fig. 13). The ST segment often elevates, forming an upward slope which becomes progressively steeper as it merges with the T waves.<sup>3</sup> All these changes are normal and have no clinical significance whatsoever.<sup>16</sup>



Figure 13: ECG during exercise. T waves are large and opposite in polarity to QRS complexes. P waves are no longer visible as they are incorporated in the preceding T waves. Line bar indicates 1 second.

## CONCLUSION

Dysrhythmias can be divided according to their origin into four groups: SA nodal, atrial myocardial, AV nodal and ventricular myocardial dysrhythmias. This classification helps to understand the changes these dysrhythmias cause on the ECG. The equine clinician is faced with a wide variety of dysrhythmias, of which a number are normal and caused by a high parasympathetic tone at rest in horses.<sup>2</sup> Exercise ECG recordings can help to make the distinction between physiological and pathological dysrhythmias. On these recordings, caution should be made for misinterpreting movement artefacts. Exercise or stress cause changes in the P and T waves on the recording but these changes have no clinical significance. With a systematic approach to evaluate an ECG recording, mistakes can be largely avoided.

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# CHAPTER 2

## SCIENTIFIC AIMS



The general aim of this PhD study was to explore new diagnostic electrocardiographic criteria and techniques in horses. Despite great advances made in electrocardiography in human and small animal medicine, electrocardiography in horses has been poorly developed. This is partly due to the depolarization process in horses that does not allow the construction of a mean electrical axis. In addition, diagnostic criteria for specific dysrhythmias in horses are often poorly described, which might result in wrong or missed diagnoses. In order to increase the refinement of diagnostics based on surface ECG recordings, more detailed studies are needed to investigate the presence of abnormalities on the equine ECG, related to specific diseases. Development of new recording techniques could further contribute to a better diagnosis and understanding of equine dysrhythmias.

The first part of this dissertation was devoted to the study of the use of a surface ECG recording, recorded in a standardized manner, for diagnosis of cardiac disease. For this purpose, standardized surface ECGs were recorded for in depth analyses from horses with a disease that affects the heart. Atrial fibrillation is clinically the most important supraventricular dysrhythmia in horses and is sometimes associated with incoordination, collapse or even sudden death during exercise. Standardised ECG recordings during exercise in horses with atrial fibrillation might reveal the cause for these signs. Therefore, the **first objective** was to evaluate the diagnostic and clinical value of exercise ECG recordings in horses with atrial fibrillation. Atypical myopathy is a highly fatal disease primarily affecting skeletal muscles. Although postmortem examinations and the occasional presence of dysrhythmias indicate the presence of cardiac damage, the exact impact and mechanism are still poorly understood. The **second objective** was to assess the potential of ECG recordings to detect the effect of atypical myopathy on the heart.

In the second part, new electrocardiographic recording techniques that allow for a better recording of atrial electrical activity compared with surface ECG recordings were explored and evaluated. In human medicine, esophageal and intra-atrial recordings have greatly advanced the understanding of dysrhythmias because of their ability to better identify the atrial depolarization. In horses, the clinical use of electrocardiography is still limited to surface ECG recordings. Therefore, the **third and fourth objective** were to record cardiac electrical activity from within the esophagus and from within the atria using esophageal and intra-atrial electrodes, respectively.



# SECTION 1

## EQUINE ELECTROCARDIOGRAPHY IN DISEASES AFFECTING THE HEART



## CHAPTER 3

# ELECTROCARDIOGRAPHY IN HORSES WITH ATRIAL FIBRILLATION



# VENTRICULAR RESPONSE DURING LUNGING EXERCISE IN HORSES WITH LONE ATRIAL FIBRILLATION

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Ventricular response during lunging exercise in horses with lone atrial fibrillation.  
Equine Veterinary Journal, accepted, online.

## SUMMARY

The purpose of this study was to investigate the ventricular response in horses with lone atrial fibrillation (AF) during exercise. In 43 horses diagnosed with lone AF a modified base-apex electrocardiogram was recorded at rest, during a standardized lunging exercise test and during recovery. All horses showed a disproportionate tachycardia in response to an increase in sympathetic tone. Ventricular premature depolarizations were present in 81% of the horses, broad QRS complexes with R-on-T morphology in 33%. The origin of this high number of abnormal QRS complexes cannot be determined from surface ECG recordings and needs further investigation. QRS broadening and R-on-T are considered risk factors for the development of ventricular tachydysrhythmias and might explain the signs of incoordination, collapse and sudden death that are sometimes reported in horses with AF.

## INTRODUCTION

With a prevalence of about 2.5%<sup>1</sup>, atrial fibrillation (AF) is the most important dysrhythmia affecting performance in horses. During AF in horses, multiple wavelets propagate through the atria at a rate of approximately 300 to 500 pulses per minute.<sup>2,3</sup> The high parasympathetic tone in horses with lone AF causes the atrioventricular (AV) node to block most of these impulses, resulting in a normal ventricular rate at rest. The chaotic self-sustained electrical activity in the fibrillating atria causes independent activation of individual muscle fibers rather than the synchronous contraction seen during normal sinus rhythm.<sup>4</sup> As a consequence, atrial contribution to ventricular filling is lost, causing a decrease in stroke volume, especially during exercise. In addition, sympathetic tone prevails during exercise, reducing the blocking function of the AV node. This causes many of the atrial fibrillatory impulses to be conducted to the ventricles, resulting in a disproportionate tachycardia. Both factors reduce cardiac function and therefore athletic ability. Depending on the exercise load, AF can be an incidental finding or can result in performance loss or in signs of weakness and incoordination (9%) or even collapse (2%) during work.<sup>5</sup>

Although numerous studies have been dedicated to AF and in particular its treatment options, limited information is available concerning electrocardiography (ECG) during exercise in horses with AF.<sup>6-9</sup> The aim of this paper was to report on the ventricular response and dysrhythmias in horses with lone AF during a standardized lunging exercise test.

## MATERIALS & METHODS

### STUDY POPULATION

Forty-three horses that were presented at the Department of Large Animal Internal Medicine, Ghent University for cardiac examination and were diagnosed with lone atrial fibrillation were included in this study.

Horses (17 mares, 5 stallions, 21 geldings; 39 warmbloods, 1 Friesian, 1 Anglo Arabian, 2 French Trotters) had an age of  $10.6 \pm 3.6$  years (mean  $\pm$  SD) (range 4-20 years), a height of  $170.2 \pm 6.1$  cm (range 152-181 cm) and a body weight of  $584.5 \pm 54.1$  kg (range 468-710 kg). Presumptive AF duration was three weeks to one year; in three horses AF duration was not known. Horses were used for dressage (n=7), jumping (n=21), both (n=3), eventing (n=2), recreational (n=6), trotting (n=2), cross-country (n=1) or driving (n=1). Presenting signs were performance reduction (n=28), epistaxis (n=3) and weakness and collapse (n=1). Eleven horses showed no signs.

In 36 horses, plasma ionized calcium, potassium and magnesium concentrations were determined. Thirty-six horses were successfully converted using transvenous electrical conversion (TVEC) (n=33) or quinidine sulphate (n=3). Three horses failed to convert by TVEC. In four horses no treatment was initiated.

### ELECTROCARDIOGRAPHY

Modified base-apex ECG was performed using a Televet 100<sup>®</sup> recording system<sup>a</sup> as described elsewhere.<sup>10</sup> Briefly, four self-adhesive electrodes were positioned under a girth<sup>b</sup> in a modified base-apex configuration: the red electrode was positioned 15 cm right from the withers, the green electrode on the thorax caudal to the left elbow. The yellow electrode was placed 10 cm above the green one. The reference electrode was positioned 15 cm left from the withers. All electrodes were connected to the recording device in the girth. The recorded ECG was visualized in real time on a laptop computer and the signal was digitally stored to allow offline analysis.

### EXERCISE PROTOCOL

Recording started as soon as the monitoring system was installed, including a fifteen minute recording at rest. Exercise protocol was a standardized lunging exercise test in

which horses walked for seven minutes, trotted for ten minutes, cantered for four minutes and galloped for one minute. Designated recovery period was seven minutes. The two minute walk to the exercise ring and back was included in the recording time during walk and the recovery phase, respectively.

### INTRA-ATRIAL ELECTROCARDIOGRAPHY

In 37 horses, a bipolar temporary pacing electrode<sup>c</sup> was positioned in the right atrium in the standing horse. This allowed simultaneous recording of an intra-atrial electrogram and a base-apex ECG at rest using a modified Televet 100<sup>®</sup> recorder<sup>d</sup> or Pacemaker Programmer.<sup>e</sup> The signal was digitally stored to allow offline analysis.

### DATA ANALYSIS

Offline analysis of exercise ECGs was performed by an experienced observer (TV) using dedicated software.<sup>f</sup> All recorded ECGs were of diagnostic quality. Sixteen percent of the recordings showed important motion artefacts, but still allowed accurate diagnosis. Standard gain (10mm/mV) and paper speed (25mm/s) were increased up to 20 mm/mV and 200mm/s where necessary to allow accurate analysis. Number and type of dysrhythmias were documented by visually inspecting the recorded ECGs. For each horse, the average heart rate at rest, walk, trot, canter and gallop was calculated; maximal heart rate was calculated from the single shortest RR interval obtained during the protocol. Duration of the QRS complexes and S waves was measured for 50 consecutive cycles at rest and during galloping, and for QRS complexes with an aberrant morphology (Fig. 1).



Figure 1: Electrocardiogram showing caliper placement for QRS and S wave duration for a normal complex and S wave duration for an R-on-T complex.

QRS complexes with abnormal morphology were categorized as VPDs, when changes in relative size of Q, R or S waves leading to changes in morphology of the complex were observed or when duration of the QRS complex was altered. Slight changes in QRS amplitude due to respiration were not taken into account. When the R wave of the abnormal QRS complex was projected on the T wave of the previous QRS complex, QRS complexes were categorized as 'R-on-T' complexes.

For each horse, measurements of QRS and S-wave duration for normal complexes (rest and gallop), VPDs and R-on-T complexes were averaged over the measured cycles. The resulting means were compared between the complex types by a linear mixed model with complex type as fixed categorical effect and with the horses as subjects in a repeated measurements analysis.

Atrial fibrillation cycle length (AFCL) was calculated from intra-atrial electrograms as an estimate of atrial refractoriness by measuring the interval between successive atrial depolarization waves from a 20-second window.

Individual maximal heart rate was compared to AFCL using Pearson's correlation test. Data are presented as mean  $\pm$  SD. Significance was set at  $P < 0.05$ .

## RESULTS

Three horses showed mild hypocalcaemia (1.4 mmol/L; reference range 1.5-1.8 mmol/L) and one was both hypocalcaemic (1 mmol/L; reference range 1.5-1.8 mmol/L) and hypokalemic (1.8 mmol/L; reference range 2.9-4.4 mmol/L).

Forty-two horses completed the protocol. In one horse the protocol was terminated during walking to the exercise ring because of a high heart rate (297 bpm at walk). In two trotting horses the canter and gallop were replaced by trotting at increased speeds.

Individual average heart rates at rest, walk, trot, canter and gallop are shown in Figure 2.

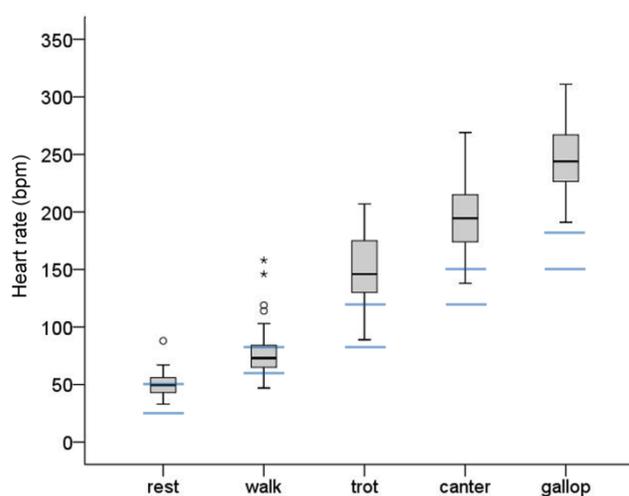


Figure 2: Heart rate in 43 horses with lone atrial fibrillation at rest and during exercise. Grey boxes indicate lower quartile to upper quartile with horizontal black line indicating median. Sample minimum and maximum are shown by whiskers. Symbols indicate outliers. Blue bars indicate typical heart rate ranges for each speed in normal horses.

At rest and during walk, 35% of the horses with AF had an average heart rate above the normal reference range (reference range rest: 25-50 bpm; reference range walk: 60-80 bpm).<sup>11</sup> During trot and canter the average heart rate was above reference range in 83% and 98% of the horses with AF, respectively (reference range trot: 80-120 bpm; canter 120-150 bpm)<sup>11</sup>. During gallop, all horses with AF in this study had an average heart rate above reference range (150-180 bpm).<sup>11</sup> Individual maximal heart rate during the lunging exercise test ranged from 248 bpm to 492 bpm (Fig. 3), while normal maximal heart rate in maximally performing horses is 240 bpm.

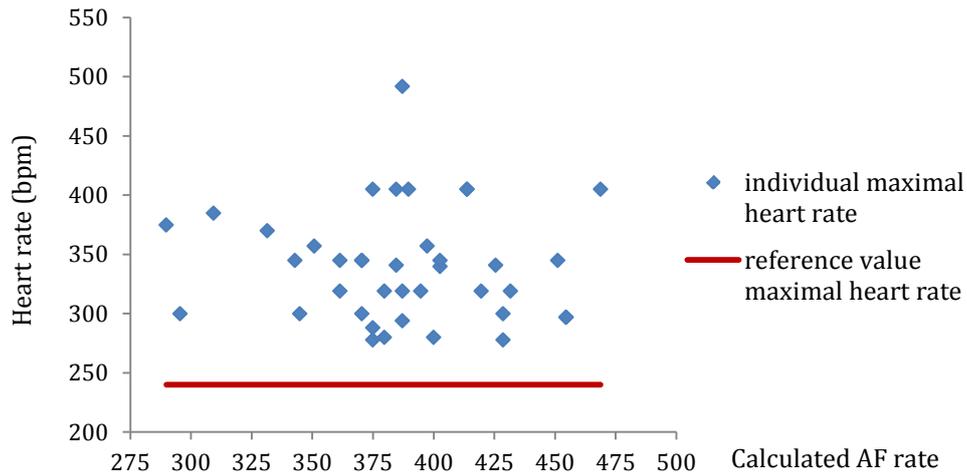


Figure 3: Individual beat-to-beat maximal heart rates during exercise as a function of calculated AF rate of 37 horses with lone atrial fibrillation.

In 81% of the horses with AF, QRS complexes with abnormal morphology, categorized as VPDs, were observed at rest (16%), during exercise (69%) or recovery phase (2%). Encountered abnormal morphologies were RS, rS, S or Rs in type. In 71% of the horses, different abnormal morphologies were observed. Both at rest and during exercise, abnormal QRS complexes were often associated with episodes of tachycardia due to increased sympathetic tone.

In 33% of the AF horses, broad QRS complexes with an R-on-T morphology were observed (Fig. 4). All QRS complexes with R-on-T morphology were associated with increased sympathetic tone: they occurred at rest when horses were aroused, or during fast galloping. Episodes with R-on-T were short lasting, varying from 1 beat to 10 consecutive beats. Often R-on-T episodes were terminated by a long RR interval. Number of episodes per horse varied from 1 to 10.

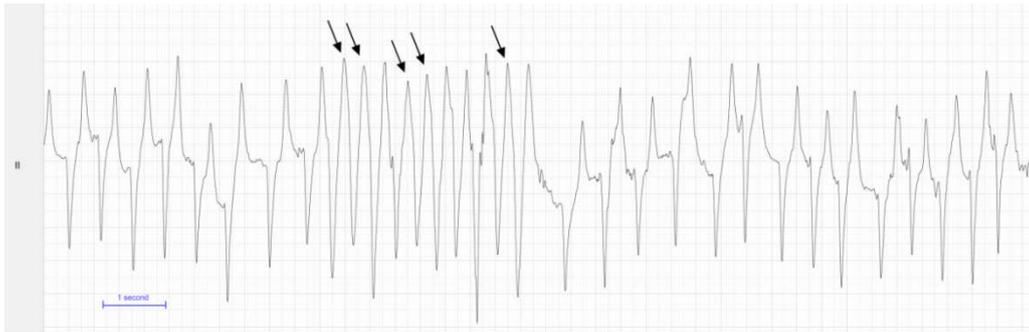


Figure 4: Electrocardiogram showing R-on-T phenomenon (arrows) during galloping in a horse with atrial fibrillation. Line bar indicates 1 second

Significant QRS shortening occurred during gallop ( $P < 0.0005$ ). Both VPDs and QRS complexes with R-on-T morphology were significantly longer than normal QRS complexes during gallop ( $P < 0.0005$ ) and shorter compared to normal QRS complexes at rest ( $P < 0.0005$ ). R-on-T complexes were not significantly different from VPDs ( $P = 1.0$ ) (Fig. 5).

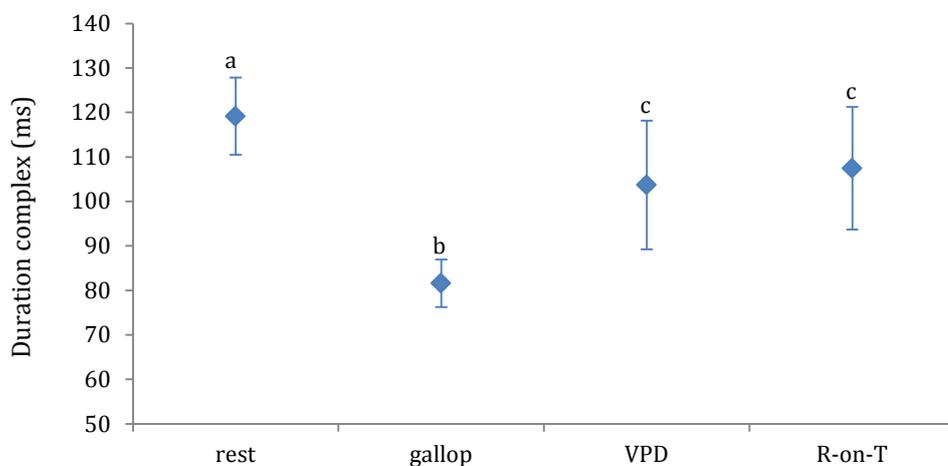


Figure 5: Duration (mean $\pm$ SD) of normal QRS, abnormal QRS and R-on-T complexes at rest and during exercise. Different letters indicate significant differences.

However, in R-on-T complexes the R wave is no longer discernible and only the S wave is measured. S wave duration was significantly larger for R-on-T complexes than for normal complexes at rest ( $P = 0.012$ ) and during gallop ( $P < 0.0005$ ). Values for R-on-T complexes were also significantly larger compared to VPDs ( $P < 0.0005$ ) (Fig. 6).

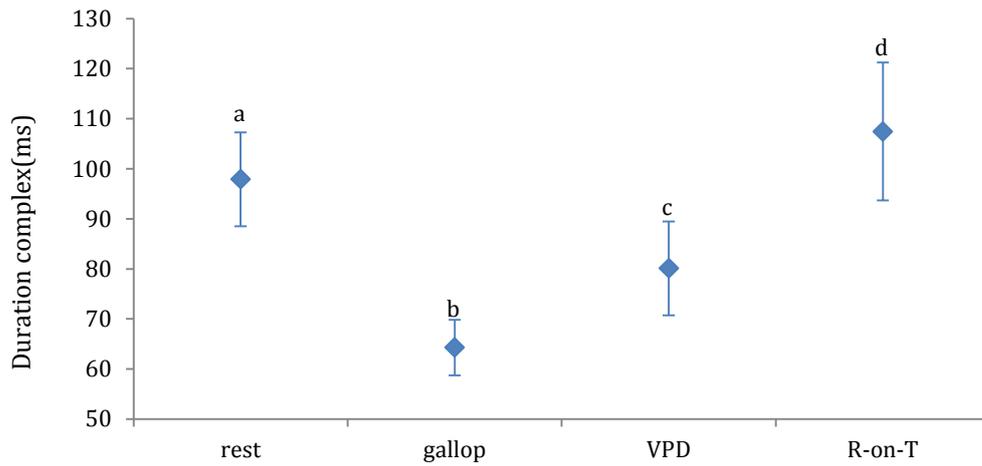


Figure 6: Duration (mean $\pm$ SD) of S waves of normal QRS, abnormal QRS and R-on-T complexes at rest and during exercise. Different letters indicate significant differences.

Average AFCL ranged from 128 to 207 ms. In eight horses recorded maximal heart rate was slightly higher than atrial fibrillation rate. Pearson's correlation test revealed no correlation between calculated AF rate at rest and individual maximal heart rate ( $P=0.591$ ).

## DISCUSSION

This study shows that in horses with lone atrial fibrillation, heart rate can raise high above the normal maximal heart rate. Excessively high heart rates are predominantly present during gallop and when horses were startled. Furthermore, QRS broadening is often found.

During atrial fibrillation, the atrioventricular (AV) node receives a high number of random electrical impulses from multiple wave fronts circulating in the atria. Ventricular response rate is determined by autonomic influences, the amount of concealed conduction and inherent AV nodal function.<sup>12,13</sup> At rest, parasympathetic tone prevails and causes depressive effects on the AV node, hyperpolarization and prolonged AV conduction time, which leads to conduction block.<sup>14,15</sup> In this situation, concealed conduction takes place: atrial impulses reach the AV node during the relative refractory phase and hence only partially penetrate into the AV node without reaching the ventricles.<sup>16</sup> Concealed conduction of an impulse affects the conduction of a subsequent impulse by delaying it, blocking it entirely or causing repetitive concealed conduction.<sup>17</sup> It is supposed that during atrial fibrillation, many of the atrial impulses are concealed within the AV node.<sup>18</sup> During exercise or stress however, vagal influence diminishes and sympathetic tone becomes predominant.<sup>19</sup> Refractory period of the AV node shortens, which decreases the occurrence of concealed conduction and hence can lead to an increase in ventricular rate.<sup>20</sup>

Another mechanism potentially contributing to increased heart rate during exercise is the dependency of the refractory period of the AV node on cycle length.<sup>21,22</sup> Functional refractory period of the AV node shortens slightly with shorter cycle lengths,<sup>23,24</sup> increasing the rate with which atrial impulses can be propagated to the ventricles. Mendez *et al.* reported the occurrence of 'abnormally' short RR intervals after early atrial premature responses.<sup>21</sup> It seemed that the AV node responded to very early reexcitation with an abrupt shortening of its refractory period, thus leading to very short RR intervals. According to the authors a possible explanation for this phenomenon could be a cumulative effect of repeated short cycles on AV nodal refractory period.

QRS complexes with abnormal morphology, categorized as VPDs, were observed in 82% of the horses with AF, with two or more different morphologies present in 73%. In comparison, the reported prevalence of VPDs during exercise in clinically healthy

dressage and show jumping horses is 5%<sup>25</sup> and 18%.<sup>26</sup> In human patients, wide QRS complexes are frequently observed in AF.<sup>27</sup> Two different processes could be causing this broadening: ventricular ectopy or aberrant intra-ventricular conduction of supraventricular impulses.<sup>28</sup> Despite the difference in origin of these two processes (atrial or ventricular), differentiation is complicated in atrial fibrillation, since the relation between atrial impulses and QRS complexes is never recognizable. The differentiation, however, has prognostic and therapeutic importance, since aberrancy will disappear when sinus rhythm is restored, whereas ventricular ectopy can significantly affect both prognosis and treatment.<sup>27,28</sup>

The differentiation is very difficult based on surface electrocardiography alone but in human medicine, several criteria have been suggested amongst which QRS contour and resemblance of the initial deflection of the anomalous beat with that of flanking normal beats seemed the most useful.<sup>28,29</sup> Some of the broad QRS complexes in the horses with AF did fulfill the criteria for aberrant conduction. However, it is unknown whether or not these criteria also apply to horses. In 73% of the horses with AF, abnormal QRS complexes were present during exercise, a period in which sympathetic tone prevails. Sympathetic stimulation accelerates AV nodal conductivity<sup>30</sup> and shortens AV nodal refractoriness. With increasing heart rates, the refractory period of the AV node can become shorter than that of left or right bundle branch, such that atrial impulses conducted through the AV node may hit one of the bundles during its refractory period. When this happens, the impulse is forced to follow an alternative pathway through the ventricles, leading to aberrant conduction caused by bundle branch block.<sup>27</sup> Twenty percent of the horses showed abnormal QRS complexes at rest. In all but one of these horses QRS abnormality was observed when horses were distressed or aroused, causing increased sympathetic tone and potentially leading to aberrant conduction. In the remaining horse, repeatedly a relatively long RR interval was followed by a short RR interval with altered QRS morphology. This phenomenon is well known in human medicine as Ashman phenomenon and is caused by aberrant intra-ventricular conduction due to right bundle branch block. This is explained by the long refractory period of the right bundle branch at slow heart rates compared to the AV node or left bundle branch,<sup>27</sup> and the fact that refractory periods are dependent upon the length of the previous RR interval. As such, when a short cycle follows a long one, the right bundle branch with its longer refractory period is still refractory, leading to a QRS complex with

a specific aberrant morphology. A similar mechanism was thought to be present in this horse (Fig. 7).

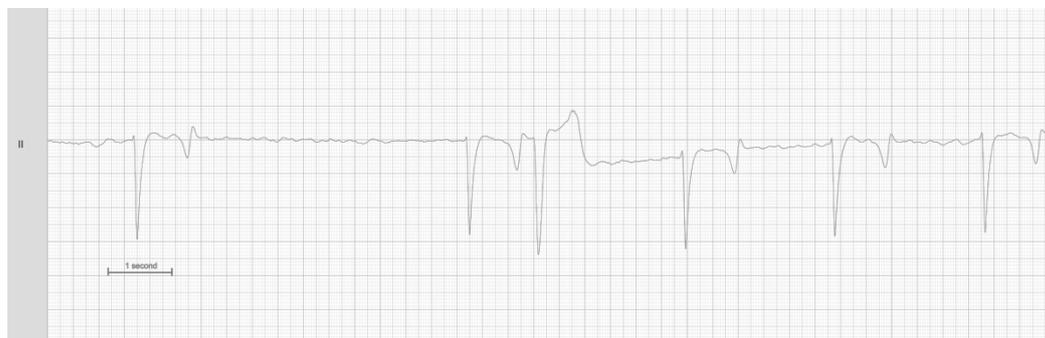


Figure 7: Electrocardiogram showing a long-short cycle with broad QRS complex terminating the sequence, suggestive of Ashman phenomenon. Line bar indicates 1 second.

In many horses, broad QRS complexes had different morphologies, which were thought to be caused by ventricular ectopy. In four horses, concomitant hypocalcaemia and/or hypokalemia was present, which may have contributed to the dysrhythmias.<sup>31,32</sup> However, abnormalities were mild, and also horses without electrolyte disturbances showed ectopic QRS complexes. Abnormal QRS complexes were most frequently observed during periods involving sympathetic stimulation. In human medicine, substantial evidence links enhanced sympathetic activity with ventricular dysrhythmias and sudden cardiac death in patients with different cardiac conditions.<sup>33</sup> Adrenergic facilitation of irregular ventricular activity has been attributed to increased automaticity, decreased diastolic threshold and decreased refractoriness. The exact importance of adrenergic tone on QRS broadening in our AF horses requires further investigation.

In 33% of the horses with AF, QRS complexes with an R-on-T morphology were observed, which means superposition of the ventricular depolarization of an ectopic ventricular beat on the T wave of the preceding beat.<sup>34,35</sup> In man, R-on-T is considered a high-grade risk factor for development of ventricular tachycardia or fibrillation.<sup>35,36</sup> However, in man, atrial fibrillation is not typically associated with R-on-T. Although the morphology of the phenomenon observed in this study in horses with AF seems to be identical to what is described as R-on-T in human medicine, it cannot be proven with

certainty whether this rhythm was supraventricular or ventricular in origin. A recent study in healthy horses reported on what was called 'torsade-like polymorphic ventricular tachycardia' (T-PMVT) in the immediate post-race period.<sup>37</sup> Although QRS complexes described in this study showed similarities with our R-on-T complexes, they occurred typically during race recovery. The authors also suggested autonomic influences as a potential cause for these dysrhythmias.

In human medicine, aberrancy is considered to be of limited clinical significance in AF, whilst VPDs are regarded as potential risk factors for the induction of ventricular tachycardia or fibrillation.<sup>28</sup> It is not known whether this is also the case for horses. Whilst R-on-T occurred relatively frequently, in none of the horses it deteriorated to ventricular fibrillation. This might suggest that R-on-T is caused by aberrancy rather than ventricular ectopy. However, signs of weakness, collapse and even sudden death have been observed in AF horses<sup>5</sup> and could also have been associated with ventricular ectopy. At this point, no definitive conclusion about the origin of broad QRS complexes can be drawn.

Individual beat-to-beat maximal heart rate was compared to AFCL in order to investigate the origin of the broad QRS complexes. If broad QRS complexes were due to bundle branch block, their origin would be supraventricular, and the shortest RR interval would approximate or be longer than the AFCL. If the shortest RR interval would be much shorter than the AFCL, broad QRS complexes would have to be ventricular in origin. Ten horses had a maximal heart rate in excess of the atrial fibrillation rate. However, differences were small and could be explained by temporal and spatial dispersion in AFCL and by the fact that increased sympathetic tone shortens AFCL.<sup>18</sup> As such, the exact origin of the abnormal QRS morphology remained unknown.

A limitation of the study is the standardized lunging exercise test performed in horses with AF, meaning that for many horses workload was below their normal level. Still, a very high prevalence of dysrhythmias was found. Although maximal exercise was not studied, higher workload might be associated with more severe rhythm disturbances.

In conclusion, horses with AF frequently develop disproportionate tachycardia during exercise. QRS broadening and R-on-T phenomenon are often found and may originate from ventricular ectopy or aberrant intra-ventricular conduction. At this point, the origin of broad QRS complexes in horses with AF remains uncertain. The high number of VPDs in these horses might indicate that some of these complexes result from aberrant

conduction rather than ventricular ectopy. However, in human medicine, R-on-T is always considered ventricular in origin. QRS broadening and R-on-T complexes might be a risk factor for exercise-associated weakness, collapse or even death. One should be aware of the high prevalence and potential risk factor of these dysrhythmias in horses with lone AF, even if they are used for low level exercise because sudden stress in a resting horse can elicit these dysrhythmias.

## FOOTNOTES

<sup>a</sup>Televet 100<sup>®</sup>, Kruuse, Marslev, Denmark

<sup>b</sup>Orthohorse<sup>®</sup>, Mainat Vet, Barcelona, Spain

<sup>c</sup>U.S.C.I. Ballinasloe, County Galways, Ireland

<sup>d</sup>K. Engel, Engel Engineering Services GmbH, Offenbach am Main, Germany

<sup>e</sup>Programmer 7990, Medtronic, Minneapolis, USA

<sup>f</sup>Televet 100<sup>®</sup> software version 4.2.0, Kruuse, Marslev, Denmark

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## CHAPTER 4

# ELECTROCARDIOGRAPHY IN HORSES WITH ATYPICAL MYOPATHY



# CARDIAC CHANGES IN HORSES WITH ATYPICAL MYOPATHY

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## SUMMARY

Limited information is available regarding the effect of atypical myopathy on cardiac function in affected and surviving horses. The purpose of this study was to describe the electrocardiographic and echocardiographic changes in the acute stage of the disease and after follow-up. Twelve horses diagnosed with AM underwent a clinical examination including electrocardiography and echocardiography. Four surviving horses were examined again after two to ten weeks. Ten horses showed ventricular premature depolarizations and in all horses a prolonged QT<sub>c</sub> interval and an abnormal myocardial wall motion were found. One horse still showed VPDs and a prolonged QT<sub>c</sub> interval at ten weeks follow-up. Results indicate that AM causes cardiac damage which can result in consistent changes on electrocardiography and echocardiography. Additional research in a larger group of horses will allow evaluation of the role of dysrhythmias on the low survival rate of horses with AM and the long-term effect of AM on cardiac function.

## INTRODUCTION

Atypical myopathy (AM) is a fatal disease occurring in grazing horses, especially during autumn and spring. The disease causes an acute degeneration of skeletal muscle, characterized clinically by weakness, stiffness, recumbency and a mortality rate of approximately 70%.<sup>1</sup> The disease was first described in the United Kingdom in 1984<sup>2,3</sup> but now is recognized in many other European countries. Furthermore, a similar seasonal pasture myopathy has been described in the United States.<sup>4</sup> The etiology of the disease remains uncertain, but recent research points toward a toxin causing mitochondrial damage and multiple acyl-CoA dehydrogenase deficiency (MADD).<sup>5-7</sup>

Postmortem examinations indicate that AM not only causes degeneration of the skeletal muscles but also may affect the myocardium. At necropsy, diffuse or multifocal pale areas may be observed in the myocardium, as well as focal areas of hemorrhage.<sup>1,4,8</sup> Histopathological changes in the myocardium are moderate to severe granular myocardial degeneration and necrosis, with lipid accumulation in the myocytes. This severe myocardial degeneration suggests that cardiac damage may be a cause for sudden death in AM-affected horses.<sup>8</sup> Most horses affected by AM have increased concentrations of plasma cardiac troponin I (cTnI), a specific biomarker of myocardial injury.<sup>9,10</sup> It is unknown to what extent the myocardium recovers in surviving horses. Previous studies have shown that tachycardia, dysrhythmias or cardiac murmurs can be found in AM horses, but detailed information is not available.<sup>1,10</sup>

The aim of our study was to investigate cardiac function in horses with AM using biomarkers, electrocardiography and echocardiography.

## MATERIALS & METHODS

### CASE SELECTION

Horses referred to the Department of Large Animal Internal Medicine, Ghent University (Belgium) with AM between 2009 and 2011 were included in this study. Inclusion criteria were housing on pasture, acute nonexertional rhabdomyolysis (i.e. myoglobinuria, stiffness, trembling, sweating, weakness, recumbency, lethargy), rapid progression and occasionally sudden death, increased plasma creatine kinase (CK) activity and availability of both ECG and cardiac ultrasound examination before initiation of medical treatment. Drugs given before referral (flunixin meglumine, butyl scopolamine, saline) were confirmed not to affect the QT interval. All horses underwent general examination on the day of arrival at the clinic. In non-survivors, the diagnosis of AM was confirmed on postmortem examinations.

### STUDY POPULATION

The study population consisted of 12 horses (7 mares, 2 geldings, 3 stallions) of different breeds (7 warmbloods, 1 Friesian, 3 ponies, 1 Arabian) aged  $3.9 \pm 2.8$  years (mean  $\pm$  SD) with a body weight of  $416 \pm 103$  kg. Upon arrival, heart rates ranged from 40 to 68 beats per minute, packed cell volume from 39 to 56%. Seven horses died or were euthanized within 1 to 4 days, 5 horses survived. Survivors were followed up after 2 to 10 weeks. At that time, they were no longer receiving any treatment.

### BIOCHEMISTRY

Ionized calcium, potassium and sodium concentrations were measured<sup>a</sup> on lithium heparine blood samples. Magnesium and CK concentrations were determined<sup>b</sup> on serum. Cardiac troponin I (cTnI) concentration was determined<sup>c</sup> on lithium heparin plasma.

### ELECTROCARDIOGRAPHY

A base-apex ECG was obtained<sup>d</sup> at the time of echocardiographic examination in standing (n=7) or recumbent (n=5) position. From 20 consecutive cardiac cycles, the QT interval was measured as the time from the onset of the QRS complex to the end of the T

wave, and the associated preceding RR interval was determined. Measurements from 10 healthy horses ( $9.6 \pm 4.4$  years,  $509 \pm 58$  kg, 7 mares, 3 geldings) at rest were used as normal control values.

## ECHOCARDIOGRAPHY

Echocardiographic studies were performed<sup>e</sup> from a right and left parasternal window ( $n=7$ ), or from only 1 side in recumbent horses ( $n=5$ ). Standard 2-dimensional and M-mode images were obtained using a phased array transducer<sup>f</sup> at a frequency of 1.7/3.4 MHz (octave harmonics). Atrial and ventricular dimensions and fractional shortening (FS) were measured in a conventional manner.<sup>11</sup> On M-mode images, time to mitral valve opening (t-MVO) was measured from a short axis image at the mitral valve level as the time interval between the R wave on the ECG and mitral valve opening. Left ventricular pre-ejection period (LVPEP) was measured as the time interval between the R wave on the ECG and aortic valve opening on long axis LV outflow tract recording. Left ventricular ejection time (LVET) was measured as the time interval between aortic valve opening and closure. Isovolumic relaxation time ( $IVRT_{M-mode}$ ) was calculated as the time from aortic valve closure to mitral valve opening.

For tissue Doppler imaging (TDI), images were recorded from a right parasternal short axis view at the papillary muscle level. Image width was decreased to  $30^\circ$  and the velocity scale ranged from  $-32$  to  $+32$  cm/s, resulting in a frame rate of 183 frames per second. During off-line analysis,<sup>g</sup> a sample area was placed in the interventricular septum (IVS) and the left ventricular free wall (LVFW) with an adapted length (11-17 mm) and width (4-6 mm) depending on wall thickness. Radial peak velocities were measured during systole ( $S_m$ ), early diastole ( $E_m$ ) and late diastole ( $A_m$ ) and the  $E_m/A_m$  ratio was calculated. Contraction duration (CD) was determined as the time from the R wave to onset of early diastolic filling (E). Isovolumic relaxation time ( $IVRT_{TDI}$ ) was measured as the time from end systole to onset E. The preceding RR interval was recorded.

For 2-dimensional speckle tracking (2DST), images were recorded from a right parasternal long axis modified 4-chamber view and a right parasternal short axis view at papillary muscle level.<sup>12</sup> Image width was decreased to  $55^\circ$ , resulting in a frame rate of 41 frames per second. Off-line analysis was performed in a semi-automated fashion using the "2D Strain" application of the ultrasound software.<sup>g</sup> A region of interest (ROI)

was drawn along the LV endocardial border in a frame at end-systole and ROI width was adjusted to wall thickness. Speckle tracking started automatically, dividing the ROI into 6 segments. Peak longitudinal (SL) strain was measured from the long axis image, circumferential (SC) and radial (SR) strain were measured from the short axis image. Contraction duration was measured as the time to peak longitudinal ( $CD_{SL}$ ), circumferential ( $CD_{SC}$ ) and radial ( $CD_{SR}$ ) strain. The mechanical dispersion of contraction was calculated as the synchrony time index (STI), defined as the time difference between the shortest and longest contraction duration of the 6 segments per loop.<sup>13</sup> All measurements were compared to those of the control group of 10 healthy horses.

### DATA ANALYSIS AND STATISTICS

QT interval was corrected for heart rate using Fridericia's correction method ( $QT_c = QT/RR^{1/3}$ ).<sup>14,15</sup> Because all echocardiographic time variables are equally influenced by heart rate, the same formula was used to correct these values, as described in human medicine.<sup>16</sup> Data are reported as mean  $\pm$  standard deviation (SD). Comparisons of means from AM horses and control horses were performed using a Student's t-test. Values of  $P < 0.05$  were considered statistically significant.

## RESULTS

Twelve horses with AM were examined. Four surviving horses were followed up after a variable period of 12 to 72 days. One surviving horse was lost to follow-up.

### BIOCHEMISTRY

At presentation, 10 horses had hyponatremia, 11 had hypocalcaemia and 1 had hypomagnesaemia. Hyperkalemia was present in 2 horses.

CK activity was increased in all horses ( $302688 \pm 265670$  mU/ml; range 21770-787000 mU/ml; reference range 10-146 mU/ml). Except for horse 11, all horses had cTnI concentrations exceeding the reference value of 0.10 ng/ml<sup>17</sup> ( $2.02 \pm 2.7$  ng/ml; range 0.12-8.95 ng/ml). In horse 5, cTnI concentration was above detection limit ( $>99.99$  ng/ml). At follow-up 2 to 10 weeks later, cTnI concentrations in surviving horses had returned to normal. There was no correlation between magnitude of cTnI concentration and survival.

### ELECTROCARDIOGRAPHY

At presentation, 10 horses had VPDs which in 5 horses were polymorphic. Mean number of VPDs per horse during a 30min recording was  $15 \pm 15$  with a range of 1 to 36. One horse also had paroxysmal ventricular tachycardia (VT). Twenty-four hours after presentation, horse 5 developed paroxysmal VT, accompanied by a deterioration of its clinical status, necessitating euthanasia. At follow-up 2 months later 1 of the surviving horses (horse 6) still had VPDs at rest and during exercise.

The QT<sub>c</sub> interval was significantly longer in horses with AM ( $P < 0.001$ ) compared to control horses ( $590 \pm 40$  ms; range 538-658 ms; reference value  $< 490$  ms) (Fig. 1). In 3 of the surviving horses, the QT<sub>c</sub> interval had returned to normal at follow-up examination 8 to 12 days later. QT<sub>c</sub> interval in horse 6 shortened but was still above that of the control group at follow-up 10 weeks later. The fifth surviving horse (horse 4) was lost to follow-up.

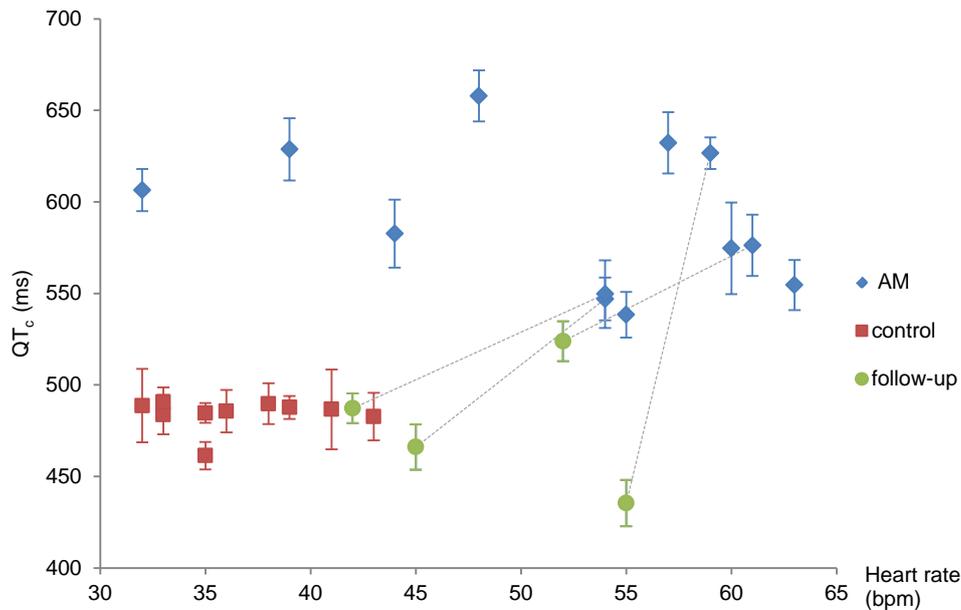


Figure 1: QT<sub>c</sub> (mean ± standard deviation) in horses with atypical myopathy compared to healthy control horses. Y-axis shows the corrected QT interval by Fridericia's method (QT<sub>c</sub>). X-axis shows heart rate. Blue symbols represent AM horses, red symbols control horses. Green symbols represent QT<sub>c</sub> at follow up in surviving horses.

## ECHOCARDIOGRAPHY

M-mode and TDI measurements for AM horses and control horses are shown in Table 1. The left atrial and left ventricular dimensions were within reference values in all horses. Visual inspection of the 2-dimensional and M-mode images showed systolic wall motion abnormality in all cases. Biphasic contraction was observed in 8 horses (Fig. 2). Biphasic contraction was most obvious in the IVS, but also was present in the LVFW in 6 horses. The IVS in the remaining 4 horses had a “plateau-like” morphology during contraction. The t-MVO<sub>c</sub> and IVRT<sub>c,M-mode</sub> were significantly longer in AM horses (P=0.017 and P<0.001, respectively), whereas LVPEP<sub>c</sub> and LVPEP/LVET were significantly shorter (P<0.001). LVET<sub>c</sub> and FS were not significantly different from control horses (P=0.363 and P=0.056, respectively).

Table 1: M-mode, TDI and 2DST echocardiographic measurements of horses with atypical myopathy compared to a healthy control group. Asterisks indicate significant differences.

Ultrasound mode	Variable	Atypical myopathy		Controls (n=10)	P
		n	mean±SD	mean±SD	
M-mode	t-MVO <sub>c</sub> (ms)	9	568±38	532±20	0.017*
	IVRT <sub>c</sub> (ms)	9	165±42	90±17	<0.001*
	LVPEP <sub>c</sub> (ms)	9	53±9	78±8	<0.001*
	LVET <sub>c</sub> (ms)	9	353±38	365±9	0.363
	LVPEP/LVET	9	0.15±0.03	0.20±0.02	<0.001*
	FS (%)	11	39.0±3.8	36.1±2.7	0.056
TDI	CD <sub>c</sub> IVS (ms)	11	563±30	526±21	0.004*
	CD <sub>c</sub> LVFW (ms)	11	554±45	533±25	0.2
	IVRT <sub>c</sub> IVS (ms)	11	224±52	133±26	<0.001*
	IVRT <sub>c</sub> LVFW (ms)	11	199±57	92±18	<0.001*
	S <sub>m</sub> IVS (cm/s)	11	7.9±2.9	5.8±0.8	0.035*
	S <sub>m</sub> LVFW (cm/s)	11	-6.9±1.4	-4.3±1.1	<0.001*
	E <sub>m</sub> IVS (cm/s)	11	7.9±2.9	13.2±2.2	<0.001*
	E <sub>m</sub> LVFW (cm/s)	11	-10.8±3.1	-14.4±1.8	0.005*
	A <sub>m</sub> IVS (cm/s)	10	5.0±3.4	3.5±2.7	0.305
	A <sub>m</sub> LVFW (cm/s)	11	-10.9±4.0	-7.3±2.0	0.019*
	E <sub>m</sub> /A <sub>m</sub> IVS	10	2.7±2.6	7.2±6.3	0.071
E <sub>m</sub> /A <sub>m</sub> LVFW	11	1.1±0.4	2.1±0.7	<0.001*	
2DST	SL (%)	7	-22.6±1.2	-24.6±1.5	0.009*
	SC (%)	7	-19.5±2.8	-20.0±1.8	0.668
	SR (%)	7	63.8±7.8	62.7±3.6	0.700
	CD <sub>SL,c</sub> (ms)	7	418±32	443±14	0.095
	CD <sub>SC,c</sub> (ms)	7	395±65	426±18	0.265
	CD <sub>SR,c</sub> (ms)	7	404±75	457±18	0.118
	STI-CD <sub>SL,c</sub> (ms)	7	102±38	57±29	0.016*
	STI-CD <sub>SC,c</sub> (ms)	7	201±101	52±20	0.008*
	STI-CD <sub>SR,c</sub> (ms)	7	80±64	43±23	0.184

2DST, 2-dimensional speckle tracking; A, late diastolic peak velocity; CD, contraction duration; c, Fridericia's correction method; E, early diastolic peak velocity; IVRT, isovolumic relaxation time; IVS, interventricular septum; LVET, left ventricular ejection time; LVFW, left ventricular free wall; LVPEP, left ventricular pre-ejection period; S<sub>m</sub>, systolic peak velocity; SC, peak circumferential strain; SD, standard deviation; SL, peak longitudinal strain; SR, peak radial strain; STI, synchronicity time index; TDI, tissue Doppler imaging; t-MVO, time to mitral valve opening

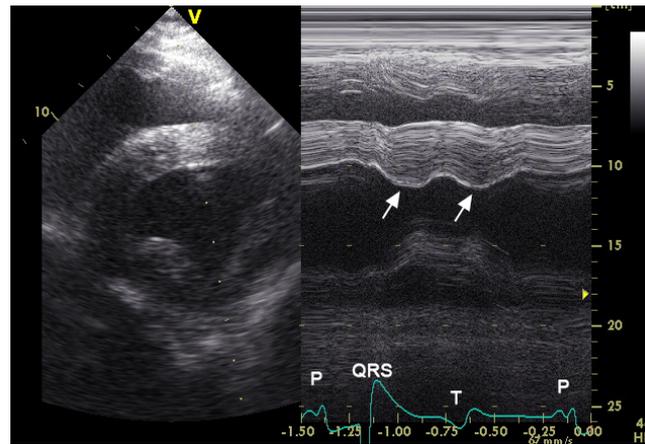


Figure 2: Short-axis 2D (left panel) and M-mode (right panel) image at papillary muscle level, showing biphasic contraction of the interventricular septum.

Biphasic contraction was evident on TDI (Fig. 3-4). In AM horses,  $CD_c$  was significantly longer in IVS ( $P=0.004$ ) but not in the LVFW ( $P=0.2$ ).  $IVRT_{c\ TDI}$  was significantly longer in both the IVS and LVFW ( $P<0.001$ ).  $S_m$  was significantly higher in both the IVS ( $P<0.001$ ) and LVFW ( $P<0.035$ ). The  $E_m/A_m$  ratio was significantly lower in the LVFW ( $P<0.001$ ) but not in the IVS ( $P=0.071$ ), whereas  $E_m$  was significantly lower in both the IVS ( $P<0.001$ ) and LVFW ( $P=0.005$ ).

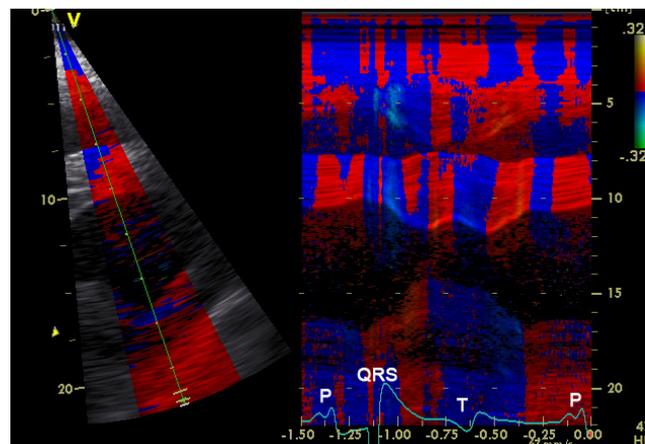


Figure 3: Short-axis 2D image at papillary muscle level with tissue Doppler imaging (TDI). The biphasic wall motion in the interventricular septum is characterized by the alternation of red and blue TDI color codes, indicating wall motion velocities towards and away from the transducer, respectively.

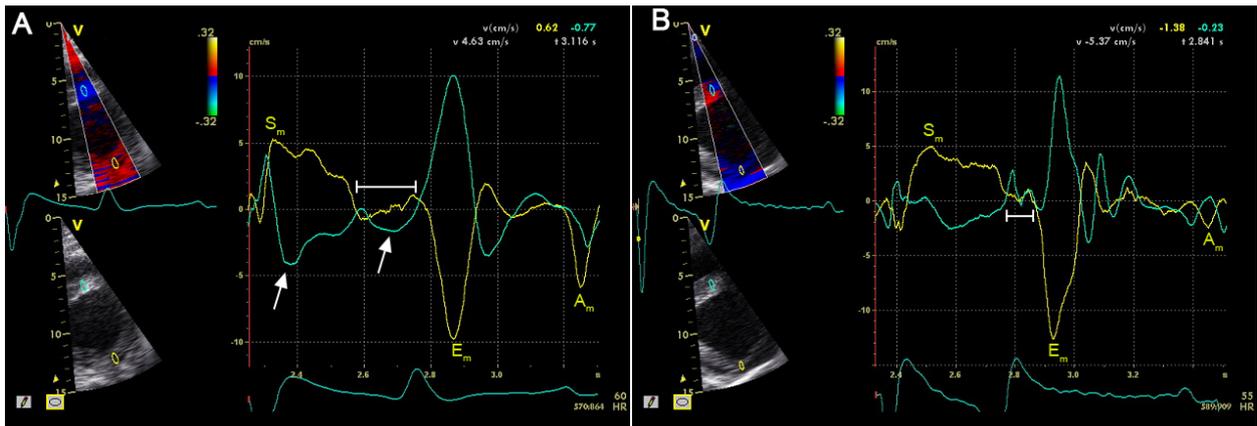


Figure 4: Wall motion velocity curve (cm/s) obtained by TDI at papillary muscle level. The ECG is displayed at the bottom. A region of interest has been placed in the left ventricular myocardium (yellow) and the interventricular septum (green).  $S_m$  represents peak radial wall motion velocity during systole,  $E_m$  represents peak radial wall motion velocity during early diastole;  $A_m$  represents peak radial wall motion velocity during late diastole. **A:** The biphasic contraction of the septum is seen as two separate negative velocity peaks during systole, demonstrated by white arrows. The prolonged isovolumic relaxation time (IVRT) is shown by a white horizontal bar. **B:** At day 11, the biphasic contraction and prolonged IVRT are no longer present.

The prolonged contraction and biphasic wall motion also were visible in the 2DST strain curves (Fig. 5). Peak SC and SR were not different from the control group, but SL was significantly lower in AM horses ( $P=0.009$ ). Although global  $CD_{SL}$ ,  $CD_{SC}$  and  $CD_{SR}$  were not prolonged, there was increased mechanical dispersion of contraction among the 6 segments per view. STI of  $CD_{SL}$  and  $CD_{SC}$  were significantly longer in AM horses, whereas the STI of  $CD_{SR}$  was not significantly different.

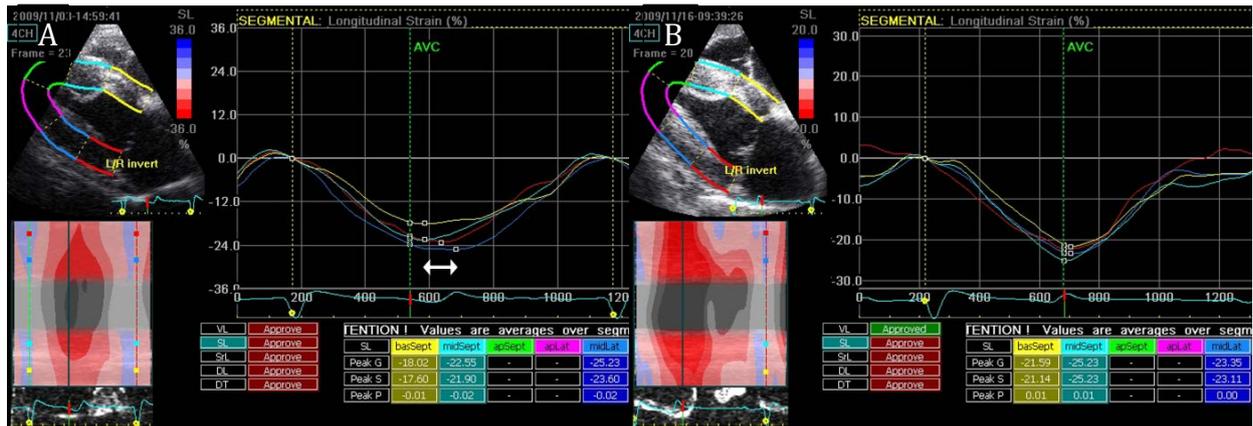


Figure 5: Longitudinal strain curve (%) obtained by 2DST from a right parasternal long axis modified four-chamber view. The ECG is displayed at the bottom. A region of interest (ROI) has been positioned on the myocardium, which is automatically divided into six segments. **A.** Mechanical dispersion is evident as the difference between shortest and longest time to peak strain (white arrow). **B.** At day 14, mechanical dispersion is no longer present.

## DISCUSSION

Our study confirms the presence of cardiac damage in horses with AM, as previously described.<sup>8</sup> Ten out of 12 horses had VPDs, and all but 1 horse had increased concentrations of cTnI on admission, indicating cardiac cellular injury. We did not find an association between the increase in cTnI concentrations and survival.

In addition, we found consistent alterations on ECG recordings and cardiac ultrasound examination. All horses had prolonged QT<sub>c</sub> intervals in association with abnormal systolic motion of the left ventricle. The QT interval represents the time between the onset of depolarization and end of repolarization in the ventricles. Because AM horses usually have increased heart rates and because physiological QT shortening occurs at increased heart rates, QT correction is required to compare intervals regardless of heart rate.<sup>14,15</sup> In humans, QT interval is known to increase with age and body mass index.<sup>18</sup> AM horses were younger and had lower body weight than control horses. However, all AM horses showed significantly longer QT<sub>c</sub> intervals, indicating prolonged ventricular repolarization. To our knowledge, this is the first time that long QT<sub>c</sub> interval has been reported in horses with cardiomyopathy. In human medicine, lengthening of the QT interval is well known and described as 'long QT syndrome' (LQTS). Two forms of LQTS exist: inherited LQTS and acquired QT prolongation. The inherited form is caused by mutations in the genes that encode ion channel proteins, causing a maintained inward current of sodium at depolarized voltages or a decrease in delayed rectifier potassium channel currents.<sup>19</sup> Both defects lead to prolongation of ventricular repolarization, which translates into QT prolongation on the electrocardiogram. The acquired form mainly has been associated with exposure to a wide variety of cardiac and noncardiac drugs,<sup>19</sup> but also with electrolyte imbalances and toxins such as cocaine and organophosphate compounds.<sup>20</sup> Abnormalities in ionic currents, mainly due to blocking or inhibiting potassium channels, may cause QT prolongation in the acquired form.<sup>19,21</sup> The origin of the long QT interval seen in AM horses is uncertain. Drug-induced prolongation seems unlikely because none of the horses had received treatment with a known QT-prolonging drug at the time of recording. Electrolyte imbalances may have played a role because hypokalemia and hypocalcaemia are known to cause QT prolongation and dysrhythmias.<sup>20,22,23</sup> However, none of the horses had hypokalemia

and 1 AM horse with normocalcaemia also showed QT prolongation, suggesting that other mechanisms may play a role. Certain toxins also can induce QT prolongation.<sup>20</sup>

The etiology of AM remains unknown, but recent research points towards a myopathy of toxic origin, affecting mitochondria.<sup>8</sup> Studies by Westermann *et al.*<sup>6</sup> and van der Kolk *et al.*<sup>7</sup> showed an acquired MADD in horses with AM, confirming the role of mitochondria in the pathophysiology of the disorder. Interestingly, in a recent study, Gélinas *et al.*<sup>24</sup> found a link between very long-chain acyl-CoA dehydrogenase deficiency (VLADD) and long QT interval in mice. They also noticed a cardiac-specific reduction of docosahexaenoic acid (DHA), an omega-3 polyunsaturated fatty acid, in the membrane phospholipids of these mice. Results suggests that DHA could have a protective effect against QT prolongation.<sup>25,26</sup> In another study in VLADD mice, Werdich *et al.*<sup>27</sup> reported alterations in intracellular calcium homeostasis and an increased ionized calcium load in the sarcoplasmic reticulum. These changes were thought to be induced by decreased adenosine triphosphate (ATP) production as a consequence of VLADD. This decrease in ATP hampers the  $\beta$ -oxidation of fatty acids and hence decreases the amount of energy available to the heart muscle cells. An increased ionized calcium load in the sarcoplasmic reticulum may increase spontaneous calcium release and lead to dysrhythmias, which were present in 10 of 12 of our AM horses. Another possible explanation for the dysrhythmias are early after-depolarizations (EADs). EADs are oscillations in membrane potential that occur when the action potential duration is increased long enough for ion channels such as L-type calcium channels to recover from inactivation and reactivate during repolarization.<sup>19,28,29</sup> They can trigger ectopic premature beats, but also increase electric heterogeneity and hence favor the development of reentrant ventricular tachycardias (VT) and Torsade de Pointes.<sup>19,21</sup> Runs of VT were present in 2 of our AM horses.

Abnormalities in ionic currents also may explain the wall motion abnormality seen on echocardiography because they can lead to prolongation of repolarization, visible on ultrasound examination as a 'plateau-like' prolonged contraction. This is supported by the fact that calcium channel blockade by verapamil in LQTS patients normalized the wall motion abnormality.<sup>30</sup> The biphasic contraction shape which was present in 8 horses also has been recognized in human LQTS patients. This was proposed to be the mechanical equivalent of an electrical EAD.<sup>30</sup> However, in these horses, the biphasic contraction usually was present in each cardiac cycle, making EAD less likely. Another

possibility is what is known in human medicine as postsystolic motion (PSM).<sup>31</sup> Although often associated with ischemia, PSM also may occur in healthy subjects. PSM also has been described in healthy horses,<sup>12,13</sup> but the duration of postsystolic contraction was much longer in AM horses. In ischemic hearts, PSM can be due to a passive inward movement of affected myocardial segments caused by adjacent normal contracting segments, or it can represent a delayed active contraction after unloading of unaffected segments and hence regional wall stress decrease.<sup>31</sup> However, a coexisting reduction in ejection velocity is obligate, which was not present in AM horses.<sup>32</sup> Therefore ischemic PSM is an unlikely explanation for the observed contraction abnormality. Based on the morphology and timing of the biphasic contraction, it is thought to be associated with aortic valve closure, causing a biphasic instead of a 'plateau-like' contraction pattern in certain segments.

TDI and 2DST measurements confirmed that the abnormal wall motion pattern was caused by delayed repolarization and thus abnormal relaxation. Similar to what has been described in human LQTS patients, the rapidity of early contraction was unaffected, as demonstrated by the shorter LVPEP and faster  $S_m$ .<sup>33,34</sup> The prolonged contraction duration was explained by a longer duration of the IVRT, with a normal ejection time. The impaired LV relaxation also was reflected by the diastolic myocardial velocities,  $E_m$  was decreased and the  $E_m/A_m$  ratio was decreased, indicating diastolic dysfunction.<sup>35,36</sup> These findings are in agreement with findings in LQTS patients in human medicine.<sup>37</sup> TDI and 2DST measurements also indicated mechanical dispersion of contraction duration. By TDI, CD was significantly longer in the IVS but not in the LVFW. By 2DST, the STI-CD for longitudinal and circumferential strain were significantly longer in AM horses. This mechanical dispersion also has been found in human LQTS patients and probably reflects electrical dispersion of repolarization.<sup>38</sup> The ion channels are not homogeneously distributed throughout the myocardium and thus a non-homogeneous prolongation of action potential duration may occur. The dispersion of repolarization increases the risk of ventricular dysrhythmias such as Torsades de Pointes. In the AM horses, CD was longer in the IVS compared to the LVFW. Similar results were found in human LQTS patients, and were attributed to longer action potential duration of the subendocardial Purkinje cells and midmyocardial M-cells which are located in the IVS.<sup>37</sup> Although FS, SR and SC were normal, SL was significantly lower in AM horses, although still within the reference range. Because longitudinal fibers are predominantly located

subendocardially, this transmural dispersion probably explains why longitudinal function was more affected both in human LQTS patients and AM horses.

Four of the surviving horses were followed up after a variable period. In all horses, cTnI concentrations returned to normal and the abnormal myocardial motion disappeared. One of the horses still showed VPDs and a QT<sub>c</sub> interval that, although shortened, remained above the reference range. There was no evidence of myocardial fibrosis on repeated echocardiographic examinations in this horse.

The number of surviving horses for follow-up was very limited, so conclusions on surviving horses must be interpreted with caution. Additional research in a larger group of horses with a longer follow-up period is necessary to evaluate the long-term consequences of AM on cardiac function and the contribution of cardiac damage to the low survival rate. ECG recordings at the time of death might elucidate causes of sudden death associated with AM. Another limitation was the relatively low number of horses in which a full cardiac examination could be performed before initiation of treatment. However, findings were very consistent in all AM horses. Horses in the control group were not age and body weight matched to AM horses, which might be important because the QT interval is positively correlated with age and body weight.<sup>18</sup> However, AM horses had longer QT intervals even though they were younger and smaller.

In conclusion, AM induces myocardial damage in horses, which can lead to consistent electrocardiographic and echocardiographic abnormalities. The exact pathophysiology remains to be elucidated, but MADD and abnormalities in ionic currents may play an important role. In 1 horse, the presence of VPDs and mildly prolonged QT<sub>c</sub> at follow-up 2 months later suggested that full recovery had not occurred. Additional research in a larger group of horses with a longer follow-up period is necessary to evaluate the long-term consequences of AM on cardiac function and the role of dysrhythmias in the low survival rate.

## FOOTNOTES

<sup>a</sup>AVL 9180 Electrolyte Analyser, Roche Diagnostics, Vilvoorde, Belgium

<sup>b</sup>Spotchem SP-4420, Arkray Europe, Amstelveen, The Netherlands

<sup>c</sup>Acces Accu-TnI, Beckman Coulter Inc, Fullerton, CA, United States of America

<sup>d</sup>Televet 100<sup>®</sup> Version 4.1.3., Kruuse, Marslev, Denmark

<sup>e</sup>GE Vivid 7 Pro, GE Healthcare, Horten, Norway

<sup>f</sup>3S Phased Array Transducer, GE Healthcare, Horten, Norway

<sup>g</sup>EchoPAC Software Version 108.1.5, GE Healthcare, Horten, Norway

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## SECTION 2

# NEW ELECTROCARDIOGRAPHIC RECORDING TECHNIQUES IN HORSES



# CHAPTER 5

## ESOPHAGEAL ELECTROCARDIOGRAPHY IN HORSES



# ESOPHAGEAL ELECTROCARDIOGRAPHY IN HEALTHY HORSES

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## SUMMARY

This study investigates the feasibility of esophageal electrocardiography in horses and its ability to magnify P waves with respect to the QRS complex. Bipolar and unipolar ECGs were made using surface and esophageal electrodes. Esophageal, combined surface-esophageal and unipolar recordings were made consecutively at different electrode positions and in different recording combinations, while simultaneously a base-apex surface ECG was recorded for comparison. Amplitudes of P, Q, R, S and T waves were measured from three different cardiac cycles for each electrode position and recording configuration. Esophageal electrocardiography was feasible in all horses. The ratio between the P wave and QRS complex magnitudes was significantly larger for intra-esophageal recordings with an interelectrode distance of 10 cm at HW<sub>+10</sub>, compared to base-apex and unipolar recordings. Results show that esophageal electrocardiography is effective in magnifying P waves with respect to the QRS complex and as such is promising for the differentiation between supraventricular and ventricular tachydysrhythmias.

## INTRODUCTION

Surface ECG is the standard method to assess cardiac rate and rhythm in horses.<sup>1-4</sup> However, it can be challenging to distinguish supraventricular from ventricular tachydysrhythmias due to drowning of the atrial P wave into the much larger ventricular complex. Selective magnification of the P wave might resolve this problem and could help in the correct diagnosis and classification of tachydysrhythmias.

In human medicine, the value of esophageal ECG recording in the identification of atrial activity and diagnosis of dysrhythmias has been recognized for many years.<sup>5,6</sup> Due to the proximity of the left atrium to the esophagus, P waves are magnified which facilitates P wave identification. As such, esophageal electrocardiography is used for diagnosis of supraventricular dysrhythmias, localization of ectopic foci and therapeutic atrial pacing.<sup>7-9</sup>

To our knowledge, no information is available about esophageal ECG in horses. The goal of this study was to assess the feasibility of esophageal ECG recording in horses and to determine optimal electrode positions for obtaining large P waves. Esophageal ECG was compared to base-apex surface ECG recordings as a 'gold standard' and to unipolar ECG recordings.

## MATERIALS & METHODS

### STUDY POPULATION

The study population consisted of 21 healthy horses with a height of  $161\pm 7$  cm and weight of  $546\pm 50$  kg (mean $\pm$ SD). Animal handling and care was performed following the guidelines of the local ethical committee.

### SURFACE AND ESOPHAGEAL ECG RECORDINGS

For esophageal recordings, an 18F (6 mm), 254 cm quadripolar esophageal catheter<sup>a</sup> was used. On its tip, four 12 mm electrodes spaced 10 cm apart were present, referred to as distal (tip), mid-distal, mid-proximal and proximal. First, a short naso-esophageal tube (105 cm length, 15 mm diameter) was placed. Subsequently, the esophageal catheter was inserted through the tube into the esophagus until resistance precluded further insertion. Catheter depth was measured in cm as the distance between the catheter tip and the nostrils. In order to correct for the height of the horses, catheter position was expressed in cm relative to the height at the withers (HW<sub>+/-cm</sub>).

At maximal depth, three intra-esophageal and three combined esophageal-surface ECGs were recorded consecutively. The first intra-esophageal recording (E/E) was made between the proximal (negative) and distal (positive) electrode on the esophageal catheter (interelectrode distance of 30 cm, referred to as E/E<sub>30</sub>). The second and third intra-esophageal recordings were between the proximal (negative) and mid-distal (E/E<sub>20</sub>) or mid-proximal (E/E<sub>10</sub>) (positive) electrode, respectively. For combined esophageal-surface recordings (E/S), three self-adhesive skin electrodes were placed on the left thorax: five cm behind the border of the triceps muscle at the level of the shoulder joint (mid) and ten cm above (high) and below (low) this position. Recordings were made between the proximal electrode of the esophageal catheter and each one of the three surface electrodes, referred to as 'E/S<sub>high</sub>', 'E/S<sub>mid</sub>' and 'E/S<sub>low</sub>'.

After recording at the maximal insertion depth, the esophageal catheter was gradually withdrawn while recordings from all six electrode configurations were made every ten cm. If on visual inspection of the recorded ECG large P wave amplitudes were noticed, horses were walked at hand for recording of all combinations during physical

movement. At a catheter depth of HW<sub>-80</sub> the last recordings were made, after which the esophageal catheter and the naso-esophageal tube were removed.

A simultaneous base-apex ECG was recorded continuously between the lower third of the right jugular groove and the left thorax behind the olecranon. ECGs were digitally stored on an ECG recording device<sup>b</sup> modified<sup>c</sup> to record two fully independent bipolar leads with a neutral electrode on the right side of the withers. All ECGs were recorded with a bandwidth of 0.05 to 100 Hz.

## UNIPOLAR SURFACE ECG RECORDINGS

Unipolar recordings (U) were made using an ECG recording device.<sup>d</sup> Using the same three surface electrodes as for the E/S recordings, three consecutive unipolar recordings were made, referred to as 'U<sub>high</sub>', 'U<sub>mid</sub>' and 'U<sub>low</sub>'.

## RADIOGRAPHY

Thorax radiographies were taken in two horses with the catheter positioned at HW or HW<sub>-10</sub> to determine the exact position of the four esophageal electrodes with respect to the heart.

## ECG ANALYSIS

ECGs were analyzed at 40 mm/mV gain and 50 mm/s speed. For every recording, amplitudes of P, Q, R, S and T waves of three consecutive cardiac cycles were measured and a mean value calculated. If the P wave consisted of two deflections, the first deflection was called 'P<sub>1</sub>' and the second 'P<sub>2</sub>'. If it only consisted of one deflection, P<sub>1</sub> was given a value of zero. According to international agreements, an initial negative deflection of a QRS complex is a 'Q wave', positive deflections are 'R waves' and negative deflections after a positive deflection are 'S waves'. For QRS morphology description, the wave of the QRS complex with the largest amplitude was given a capital, the other waves were written in small. If the T wave consisted of two deflections, the first deflection was called 'T<sub>1</sub>' and the second 'T<sub>2</sub>'. If it only consisted of one deflection, T<sub>2</sub> was given a value of zero.

For every recording configuration, the maximal value for the P wave was averaged for all horses ('mean maximal P wave'), and this value was used to compare different recording

configurations. The magnitude (voltage between minimal and maximal values during the wave or complex) of the P wave and the QRS complex were used for calculating the ratio between the P wave and the QRS complex ( $P/QRS_{\text{magn}}$ ). This ratio was calculated for every electrode configuration, using the mean maximal values for the P wave and QRS complex, and compared to  $P/QRS_{\text{magn}}$  for base-apex and unipolar surface recordings.

## STATISTICAL ANALYSIS

Statistical analysis was performed using dedicated computer software.<sup>e</sup> Summary statistics for the measurements were calculated (mean $\pm$ SD; n=21 horses). Linear mixed models with horse as random effect were fitted for P wave and  $P/QRS_{\text{magn}}$  to the different wave amplitudes; fixed categorical effects were recording depth and recording configuration. Multiple comparisons were adjusted according to the Bonferroni technique and the corresponding adjusted p-values were reported. The level of significance was  $\alpha=0.05$ .

## RESULTS

### FEASIBILITY OF ESOPHAGEAL ECG RECORDING

Esophageal ECG recording was well tolerated in all horses without the use of sedatives. Maximal insertion of the catheter was 210 cm (n=1), 200 cm (n=6), 190 cm (n=12), 180 cm (n=1) or 170 cm (n=1).

Good quality recordings could be obtained from all horses, but not always from all recording depths. For intra-esophageal (E/E) recordings, good quality recordings were obtained from HW<sub>+40</sub> up to HW<sub>-30</sub>, HW<sub>-40</sub> and HW<sub>-50</sub> for E/E<sub>10</sub>, E/E<sub>20</sub> and E/E<sub>30</sub>, respectively. Combined esophageal-surface (E/S) recordings of good quality could be made from HW<sub>+40</sub> up to HW<sub>-80</sub>.

Recordings during walk were of poor quality and were considered to be of no diagnostic value. However, three cardiac cycles could be analyzed in 52% of the intra-esophageal recordings and in 72% of the combined esophageal-surface recordings.



Figure 1: ECG tracing showing esophageal recording (top) versus base-apex surface recording (bottom). Note the larger P wave amplitude and reduced QRS complex and T wave amplitude on the esophageal recording compared with the surface recording.

## P WAVE

For all recording combinations, the amplitude of  $P_2$  was larger than  $P_1$ , exceptions being E/E<sub>30</sub> at HW<sub>-50</sub> and E/E<sub>10</sub> at HW.

In E/S recordings,  $P_1$  and  $P_2$  were always positive and hence had a bifid shape. In contrast, in E/E recordings  $P_2$  reached a maximal positive value around HW<sub>+10</sub>, and then with further withdrawal of the catheter reached a negative peak around HW<sub>-20</sub>. The 'level of bipolar atrial transition', the switch from a positive to a negative value, was situated between HW and HW<sub>-10</sub>. In both base-apex and unipolar recordings, P waves had a predominantly bifid shape.

Amplitude of  $P_1$  was small and variable and therefore will not be further discussed (Table 1) (All tables are provided after the discussion).

The means and standard deviations for  $P_2$  from esophageal, unipolar and base-apex recordings are shown in Fig. 2A and 2B. For all E/E recording configurations, optimal recording depth was situated at HW<sub>+10</sub>. At this recording depth,  $P_2$  for E/E<sub>30</sub> was significantly larger than at all other recording depths except HW and HW<sub>+20</sub> ( $P=0.009$ ). For E/E<sub>20</sub> it resulted in significantly larger  $P_2$  waves than at all other recording depths except HW<sub>+20</sub> ( $P=0.004$ ). For E/E<sub>10</sub>, optimal recording depths were situated at both HW<sub>+10</sub> and HW<sub>+20</sub>, where the resulting  $P_2$  waves were significantly larger ( $P=0.019$ ) than at all other recording depths except HW<sub>+30</sub> and HW<sub>+40</sub> (Fig. 2A). When mutually comparing E/E recordings, P wave amplitude for E/E<sub>30</sub> and E/E<sub>20</sub> were significantly larger than for E/E<sub>10</sub> ( $P<0.001$ ). For all E/S recordings,  $P_2$  was significantly larger at HW<sub>+10</sub> than at all other recording depths except at HW ( $P=0.025$ ) (Fig 2B). When mutually comparing E/S recordings, there were no significant differences in  $P_2$  wave amplitude. For unipolar recordings,  $U_{mid}$  resulted in the largest  $P_2$  ( $0.34\pm 0.12$  mV),  $U_{high}$  in the smallest. There were no significant differences amongst unipolar recordings. The mean  $P_2$  for base-apex recordings was  $0.19\pm 0.05$  mV. Mean  $P_2$  amplitude for different recording configurations at different recording depths are given in Table 2.

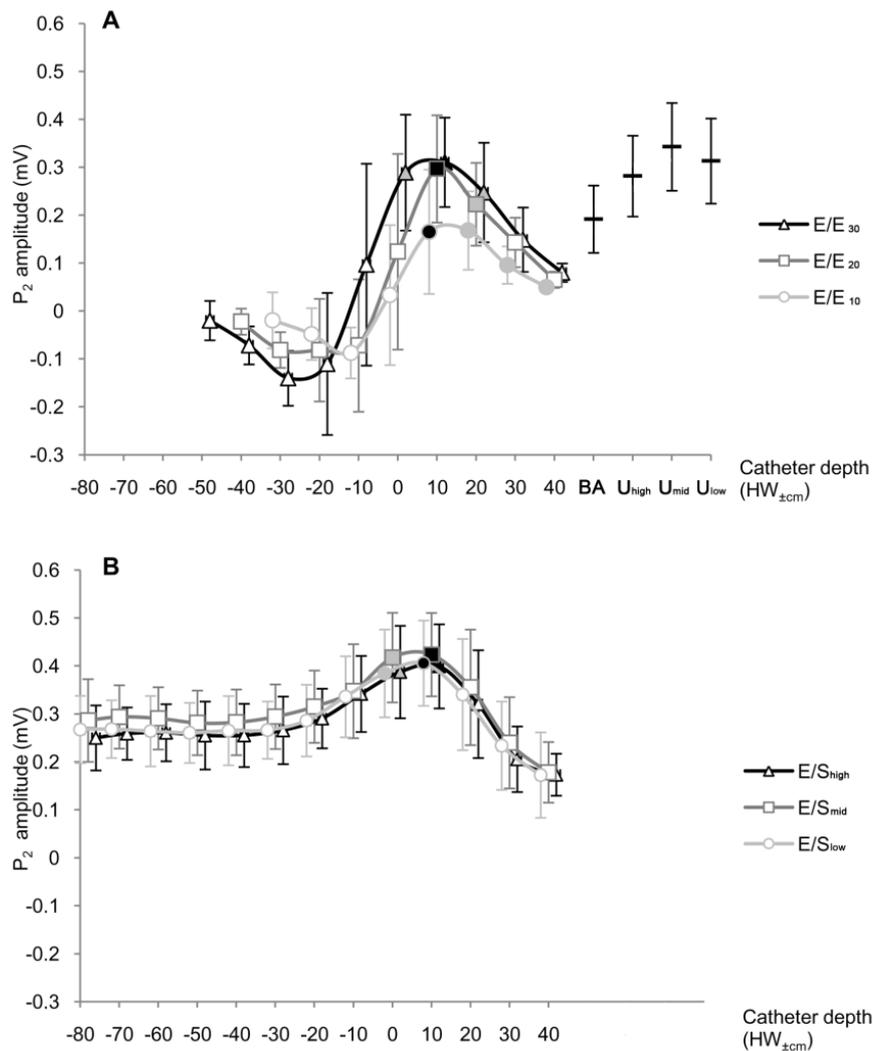


Figure 2: Mean amplitude of P<sub>2</sub> for different recording configurations at different recording depths. For each recording configuration, black symbols are significantly different from white symbols. X-axis represents catheter depth expressed as HW<sub>±cm</sub>. **(A)** P wave amplitude for intra-esophageal (E/E), base-apex (BA) and unipolar (U) recordings. **(B)** P wave amplitude for combined esophageal-surface (E/S) recordings.

Figure 3 shows the mean maximal amplitude of P<sub>2</sub> for every recording configuration. Mean maximal P<sub>2</sub> was largest for E/S recordings: significant differences were found with base-apex recordings ( $P < 0.001$ ), unipolar recordings ( $P = 0.001$ ) and E/E recordings ( $P = 0.009$ ). Except for E/E<sub>10</sub>, all E/E, all E/S and all unipolar recordings resulted in significant larger mean maximal P<sub>2</sub> compared to base-apex recordings ( $P < 0.001$ ).

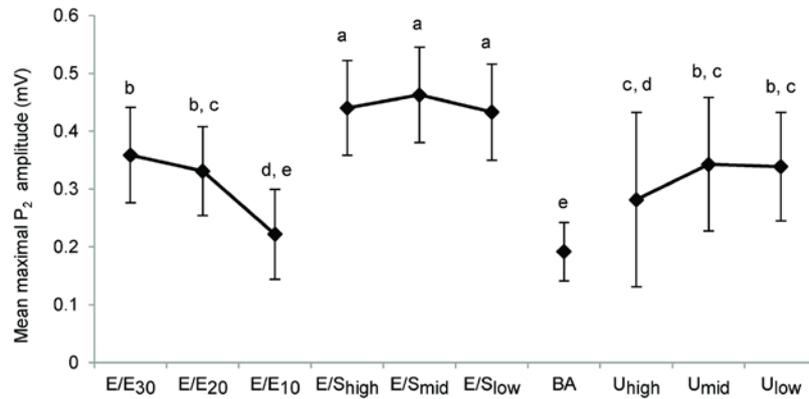


Figure 3: Mean maximal P<sub>2</sub> wave amplitude for intra-esophageal (E/E<sub>30</sub>, E/E<sub>20</sub>, E/E<sub>10</sub>), combined esophageal-surface (E/S<sub>high</sub>, E/S<sub>mid</sub>, E/S<sub>low</sub>), base-apex (BA) and unipolar recordings (U<sub>high</sub>, U<sub>mid</sub>, U<sub>low</sub>). Different letters indicate significant differences.

## QRS COMPLEX

### QRS morphology

For E/E recordings an 'rS' morphology (37%) was present at the deepest catheter insertions, which changed to a 'qR' morphology (54%) with withdrawal of the catheter. The switch from a predominantly negative ('rS') to a predominantly positive ('qR') morphology was situated around the HW point. In a small number of cases, morphology consisted of 'qrS' (7%), 'R' (1%) or 'Q' (0.8%) waves.

For E/S recordings, 'rS' morphology was highly present (94%). In a small number of cases, morphology consisted of 'Q' (3%), 'qrS' (3%) or, rarely, 'qR' waves (0.3%).

In unipolar recordings, 74% of the QRS complexes had an 'rS' morphology, 15% had a 'Q' morphology, 5% had an 'R' morphology, 4% a 'qRs' morphology and 2% a 'qR' morphology.

For base-apex recordings, 95% of the complexes had an 'rS' morphology. One horse (5%) had a QRS morphology consisting of a 'Q' wave.

### Q wave

With gradual retraction of the esophageal catheter, small Q waves appeared for E/E<sub>30</sub> and E/E<sub>20</sub> recordings at the HW point, to reach a peak at HW<sub>-20</sub> ( $-0.09 \pm 0.04$  mV) and HW<sub>-10</sub> ( $-0.07 \pm 0.06$  mV), respectively. For E/E<sub>10</sub> recordings, a Q wave already appeared at

HW<sub>+20</sub> and gradually increased until HW<sub>-30</sub> ( $-0.05 \pm 0.02$  mV), after which recording quality worsened.

For E/S recordings, Q waves became clear starting from the HW<sub>-20</sub> point. With further retraction of the esophageal catheter, Q wave amplitudes remained similar until the HW<sub>-70</sub> point, but disappeared at HW<sub>-80</sub>. The Q wave amplitude was largest for E/S<sub>low</sub> at HW<sub>-70</sub> ( $-0.07 \pm 0.28$  mV). Mean Q amplitude for different recording configurations at different recording depths are given in Table 3.

Only one horse had a Q wave in the base-apex recording configuration ( $-0.07 \pm 0.32$  mV). For unipolar recordings, Q wave was largest for U<sub>low</sub> recordings ( $-0.20 \pm 0.49$  mV) and smallest for U<sub>high</sub> recordings ( $-0.06 \pm 0.14$  mV).

### R wave

For E/E recordings, the smallest R wave amplitude was reached for E/E<sub>10</sub> at HW<sub>+40</sub> ( $0.09 \pm 0.03$  mV) (Fig. 4A). R wave amplitude became noticeably larger at catheter depths less than the HW point. The R wave amplitude was fairly constant for E/S recordings with the lowest values at the deepest catheter positions. The smallest R wave amplitude was measured for E/S<sub>low</sub> at HW<sub>+40</sub> ( $0.09 \pm 0.04$  mV) (Fig. 4B). The average R wave for base-apex recordings was  $0.28 \pm 0.13$  mV. For unipolar recordings, R wave was smallest at the U<sub>low</sub> configuration ( $0.28 \pm 0.21$  mV) (Fig 4A). Mean R amplitude for different recording configurations at different recording depths are given in Table 4.

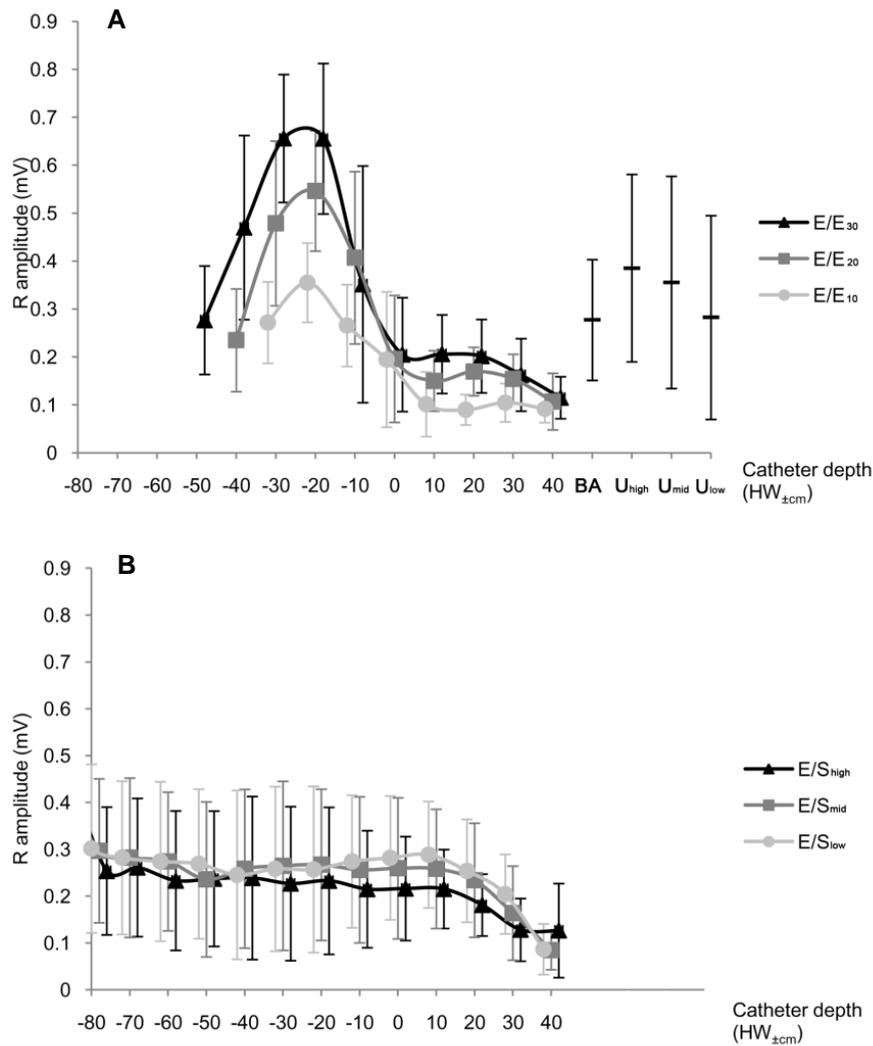


Figure 4: Mean amplitude of R waves for different recording configurations at different recording depths. X-axis represents catheter depth expressed as  $HW_{\pm cm}$ . **(A)** R wave amplitude for intra-esophageal (E/E), base-apex (BA) and unipolar (U) recordings. **(B)** R wave amplitude for combined esophageal-surface (E/S) recordings

## S wave

For E/E recordings, S waves disappeared with less deep catheter positions (Fig. 5A). For E/S recordings, S wave was smallest for E/S<sub>high</sub> at  $HW_{+40}$  ( $-0.28 \pm 0.37$  mV) (Fig. 5B). The average S wave for base-apex recordings was  $-1.23 \pm 0.42$  mV. For unipolar recordings, S wave was smallest at the U<sub>high</sub> configuration ( $-0.21 \pm 0.16$  mV) (Fig. 5A). Mean S amplitude for different recording configurations at different recording depths are given in Table 5.

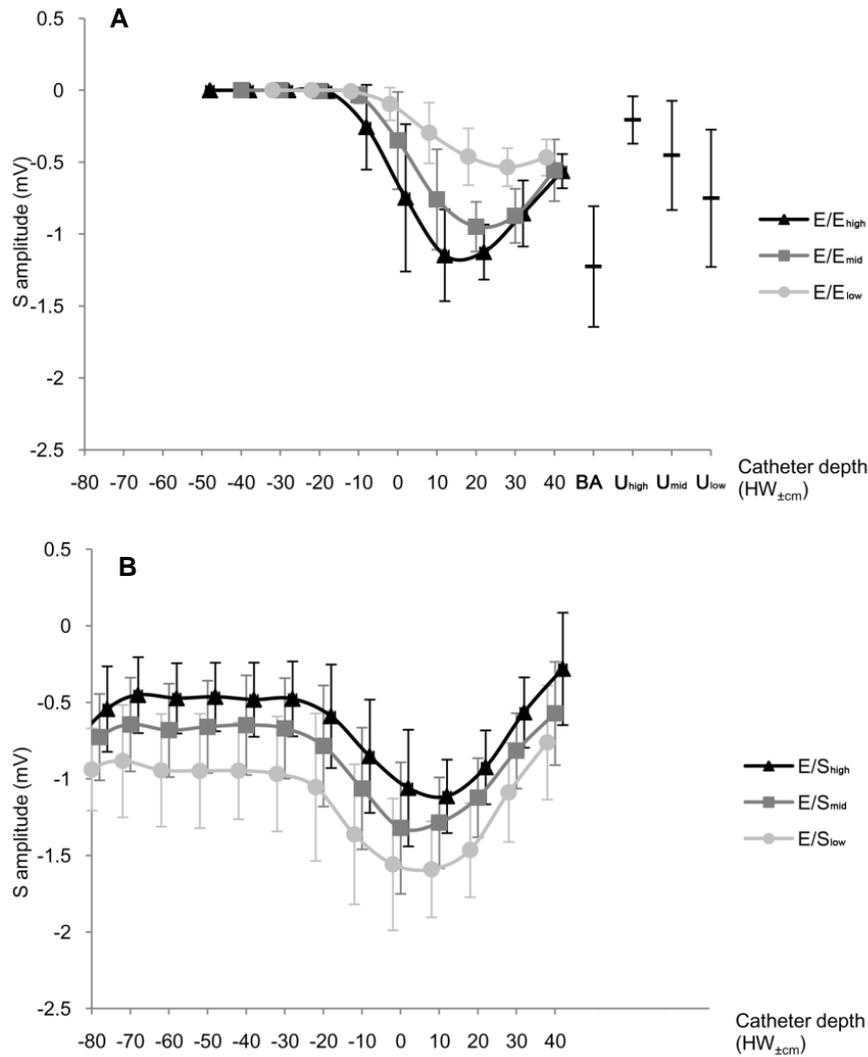


Figure 5: Mean amplitude of S waves for different recording configurations at different recording depths. X-axis represents catheter depth expressed as HW<sub>±cm</sub>. (A): S wave amplitude for E/E, BA and U recordings. (B): S wave amplitude for E/S recordings.

## T wave

For E/E recordings, the T wave was always biphasic or bifid. For E/S, unipolar and base-apex recordings, the T wave was always biphasic, with negative T<sub>1</sub> and positive T<sub>2</sub>. T<sub>1</sub> overall had the largest amplitude. Mean T<sub>1</sub> and T<sub>2</sub> amplitudes for different recording configurations at different recording depths are given in Table 6 and 7, respectively.

## P/QRS<sub>MAGN</sub>

For E/E<sub>30</sub>, P/QRS<sub>magn</sub> at HW<sub>-10</sub> was significantly larger than at all other recording depths except HW (P=0.041). For E/E<sub>20</sub>, the ratio was significantly larger at the HW position

( $P < 0.001$ ), except for recording depths  $HW_{-10}$  and  $HW_{+10}$ . For  $E/E_{10}$ , the ratio was significantly larger at  $HW_{+10}$  ( $P = 0.049$ ), except for recording depths  $HW$  and  $HW_{-10}$  (Fig. 6A). The largest  $P/QRS_{\text{magn}}$  ratio for all three  $E/E$  recording configurations was  $0.66 \pm 0.44$  mV, measured at  $E/E_{10}$ ,  $HW_{+10}$ .

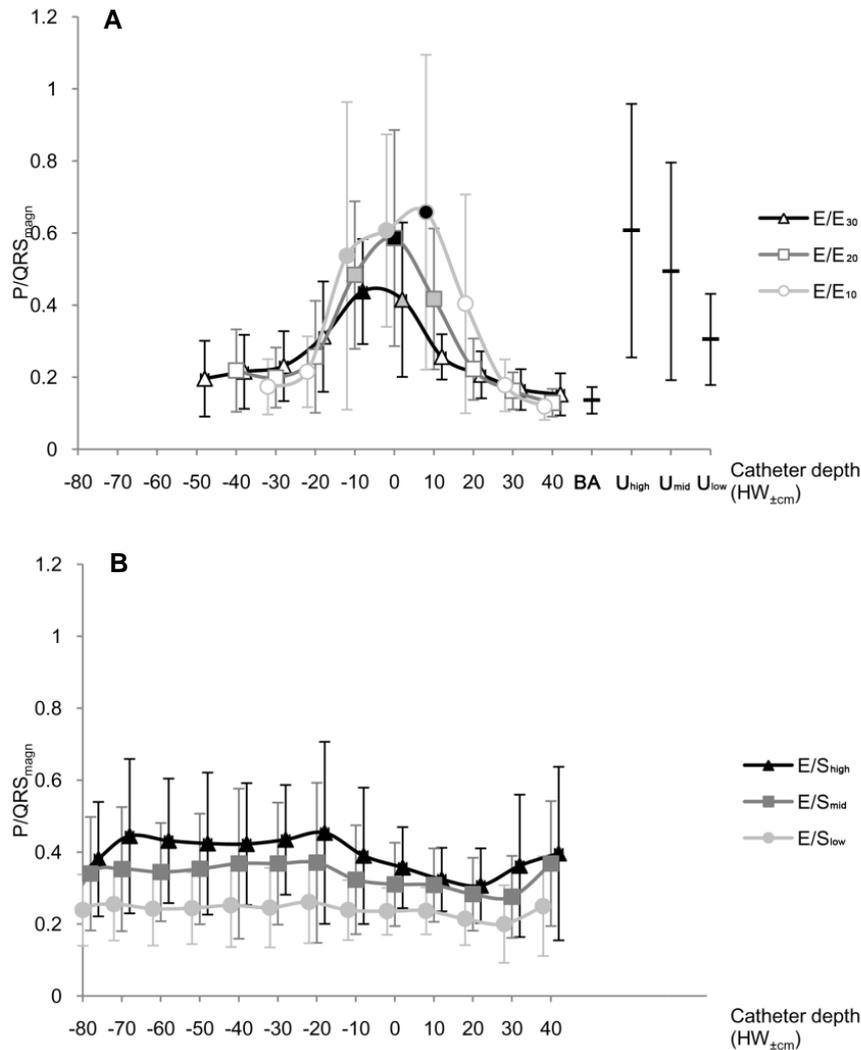


Figure 6: Mean amplitude of  $P/QRS_{\text{magn}}$  ratio for different recording configurations at different recording depths. For each recording configuration, black symbols are significantly different from white symbols. X-axis represents catheter depth expressed as  $HW \pm \text{cm}$ . (A) Magnitude of P wave with respect to magnitude of QRS complex ( $P/QRS_{\text{magn}}$ ) for E/E, BA and U recordings. (B)  $P/QRS_{\text{magn}}$  for E/S recordings.

For E/S recordings,  $P/QRS_{\text{magn}}$  tended to become larger with withdrawal of the catheter. The largest ratios for all three E/S recording configurations were measured at  $HW_{-20}$ :  $0.45 \pm 0.25$  mV,  $0.37 \pm 0.22$  mV and  $0.26 \pm 0.11$  mV for  $E/S_{\text{high}}$ ,  $E/S_{\text{mid}}$  and  $E/S_{\text{low}}$ ,

respectively (Fig. 6B). Mean amplitude of  $P_{\text{magn}}/QRS_{\text{magn}}$  ratio for different recording configurations at different recording depths is shown in Table 8.

The largest mean maximal  $P/QRS_{\text{magn}}$  ratio was obtained for E/E recordings (Fig. 7). All E/E, E/S and unipolar recordings resulted in significantly larger mean maximal  $P/QRS_{\text{magn}}$  ratios than base-apex recordings ( $P < 0.001$ ), except for  $E/S_{\text{low}}$  and  $U_{\text{low}}$  recordings.  $E/E_{10}$  was significantly larger than all other recording configurations except  $E/E_{20}$  ( $P = 0.001$ ).

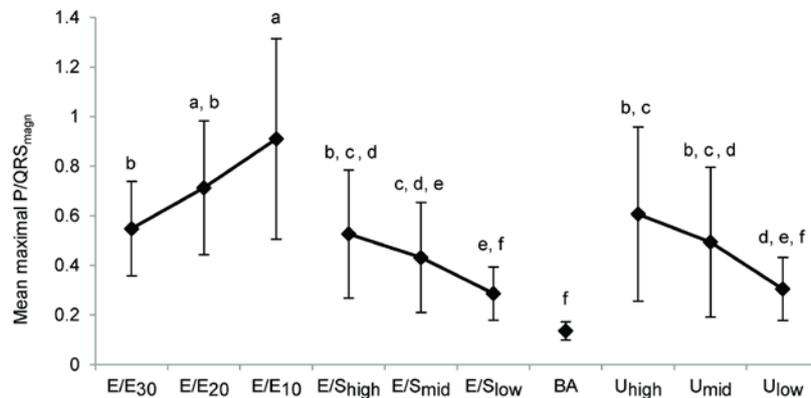


Figure 7: Mean maximal magnitude of  $P_2$  with respect to magnitude of QRS ( $P/QRS_{\text{magn}}$ ) for intra-esophageal ( $E/E_{30}$ ,  $E/E_{20}$ ,  $E/E_{10}$ ), combined esophageal-surface ( $E/S_{\text{high}}$ ,  $E/S_{\text{mid}}$ ,  $E/S_{\text{low}}$ ), base-apex (BA) and unipolar recordings ( $U_{\text{high}}$ ,  $U_{\text{mid}}$ ,  $U_{\text{low}}$ ). Different letters indicate significant differences.

## RADIOGRAPHY

In two horses, thoracic radiographs were taken with the esophageal catheter positioned at the level of bipolar atrial transition for  $E/E_{20}$ . The proximal electrode was located at the first thoracic vertebra and the mid-distal electrode at the cranial border of the aorta.

## DISCUSSION

This study demonstrates the feasibility of esophageal ECG and its ability to magnify the amplitude of the P wave compared to base-apex and unipolar surface recordings. In general, E/S recordings resulted in the largest P<sub>2</sub> wave amplitudes, while E/E recordings resulted in the largest P/QRS<sub>magn</sub>.

The esophageal catheter was successfully positioned and well tolerated in all horses without the use of sedatives. Some horses showed mild head-shaking which occasionally resulted in artefacts on the esophageal ECG. Other possible causes of baseline wander or low frequency artefacts include peristaltic movement of the esophagus, bad contact of the electrodes with the esophageal wall or respiration.<sup>10,11</sup> In esophageal recordings in man, these artefacts are reduced by a bandpass filter from 0.5 or 5 Hz up to 100 Hz and by using a preamplifier to maximize the atrial depolarization.<sup>12-14</sup> Recordings in this study were filtered with a wider bandwidth, i.e. lower cut-off frequency of only 0.05 Hz, hence low frequency artefacts due to peristalsis or respiration were not filtered out. However, esophageal ECG recording is reported to occasionally result in a greater amount of noise than surface ECG recordings.<sup>15</sup>

During walking, artefacts were more pronounced on E/S and especially E/E recordings than on base-apex recordings. This was thought to be due to movement of the esophagus in the thorax or other external influences.

One of the aims of this study was to obtain a relatively larger P wave on esophageal ECG recordings, as described in human medicine.<sup>6,12</sup> This study demonstrated that esophageal ECG is effective in magnifying the P wave amplitude. For both E/E and E/S recording configurations, the optimal recording depth was HW<sub>+10</sub>. Recording configuration E/S<sub>mid</sub> at HW<sub>+10</sub> should be used if the goal is to maximize the P wave amplitude irrespective of the QRS complex. This recording method will not only enlarge P waves, but also the QRS complexes and T waves. If P waves need to be enlarged with respect to the QRS complex, an intra-esophageal ECG should be recorded, as this will result in a significantly larger P to QRS ratio. The largest ratio is obtained with recording configurations E/E<sub>10</sub> or E/E<sub>20</sub>, at recording depth HW<sub>+10</sub>. At this position, the esophageal electrodes are situated close to the heart and well positioned in relation to the direction of the atrial depolarisation wave. This finding is in agreement with human esophageal

ECG studies.<sup>13</sup> Another agreement with studies conducted in man is the appearance of a 'level of bipolar atrial transition': a region where the atrial complex rather abruptly reverses direction.<sup>5,16</sup> On RX images in man, it was shown that this level was reached if the midpoint of the electrodes was in apposition to the left atrium. In our study, the level of bipolar atrial transition was reached at catheter depths HW and HW<sub>10</sub>. Radiographic imaging showed that the electrodes were positioned at the first thoracic vertebra (proximal) and at the cranial border of the aorta (mid-distal). We hypothesize that at this level, the mean electrical axis of the atria is perpendicular to the position of the esophageal electrodes, hence resulting in small deflections on the ECG.

In analogy with the 'level of bipolar atrial transition' found for esophageal P waves, the esophageal QRS complexes also had a 'turning point', situated around the HW point: with deeper catheter insertions, the QRS complex was predominantly negative, while with more superficial positions, the QRS complex became predominantly positive. The ventricular mean electrical axis on average runs from ventral to dorsal and from caudal to cranial.<sup>17</sup> At the deepest catheter insertions, the depolarization wave hence moves away from the positive electrode, creating a negative deflection on the ECG. If the catheter is retracted beyond the HW point, the depolarization wave moves towards the positive electrode, which results in a positive deflection on the ECG.

Maximal P wave amplitude on the intra-esophageal ECG was on average  $2.03 \pm 0.71$  times larger than on the base-apex ECG. Recording from a combined esophageal-surface ECG resulted in maximal P waves that were on average  $2.58 \pm 0.63$  times larger.  $P/QRS_{\text{magn}}$  was on average  $7.52 \pm 2.35$  larger on intra-esophageal recordings and  $4.13 \pm 2.01$  times larger on combined esophageal-surface recordings when compared to the ratio on the base-apex ECG. Similar to human medicine, esophageal ECG recording might be helpful in distinguishing supraventricular from ventricular dysrhythmias. Especially during tachydysrhythmias, atrial impulses can get buried in the ventricular depolarisation wave. With esophageal ECG it is possible to increase the ratio between P and QRS, hence facilitating the identification of P waves.

Atrial flutter and atrial fibrillation cycle length in horses are currently derived from intracardiac electrograms.<sup>18-20</sup> Cycle length measurements using esophageal ECG would considerably reduce the invasiveness of the procedure, thus enhancing its practicality. In addition, esophageal ECG studies in man have proven to elucidate atrial depolarisation and conduction,<sup>21-23</sup> an area that is still poorly understood in horses.<sup>17,24</sup> Finally,

esophageal electrodes might be used for temporary cardiac pacing.<sup>8,9,25</sup> Cardiac pacing is used in human medicine for electrophysiological evaluation and treatment of brady- and tachydysrhythmias.<sup>26,27</sup> Stimulation at the site where the amplitude of the atrial electrogram is maximal results in stable atrial capture.<sup>8</sup> The optimal electrode position for obtaining large P waves as described in our study hence might be an appropriate site for cardiac pacing in horses.

A limitation of the current study is that only healthy horses in normal sinus rhythm were studied. Atrial or ventricular ectopy is likely to alter morphology of depolarization waves on the different recordings.

In conclusion, esophageal ECG recording is a safe, simple and effective technique to record cardiac electrical activity and to amplify atrial electrical activity in healthy horses. The procedure is a promising tool for the diagnosis and distinction of supraventricular and ventricular tachydysrhythmias. Additional future applications of esophageal electrocardiography might include electrophysiological studies to investigate atrial depolarisation and conduction both in sinus rhythm and atrial fibrillation, and cardiac pacing.

## TABLES

Table 1: Mean amplitude of  $P_1$  wave for different recording configurations at different recording depths (average $\pm$ SD). Catheter depth is shown relative to height of the withers.

Catheter depth	Recording configuration					
	E/E <sub>30</sub>	E/E <sub>20</sub>	E/E <sub>10</sub>	E/S <sub>high</sub>	E/S <sub>mid</sub>	E/S <sub>low</sub>
-80	-	-	-	0.03 $\pm$ 0.09	0.02 $\pm$ 0.10	0.07 $\pm$ 0.07
-70	-	-	-	0.03 $\pm$ 0.09	0.06 $\pm$ 0.08	0.05 $\pm$ 0.09
-60	-	-	-	0.03 $\pm$ 0.08	0.05 $\pm$ 0.09	0.05 $\pm$ 0.09
-50	0 $\pm$ 0.05	-	-	0.04 $\pm$ 0.09	0.05 $\pm$ 0.08	0.04 $\pm$ 0.09
-40	0 $\pm$ 0.06	-0.01 $\pm$ 0.05	-	0.03 $\pm$ 0.09	0.05 $\pm$ 0.08	0.06 $\pm$ 0.08
-30	-0.01 $\pm$ 0.08	-0.01 $\pm$ 0.06	-0.03 $\pm$ 0.05	0.04 $\pm$ 0.09	0.04 $\pm$ 0.10	0.04 $\pm$ 0.09
-20	0.03 $\pm$ 0.10	0.02 $\pm$ 0.07	-0.02 $\pm$ 0.04	0.04 $\pm$ 0.11	0.05 $\pm$ 0.10	0.03 $\pm$ 0.11
-10	0.07 $\pm$ 0.11	0.06 $\pm$ 0.09	0.04 $\pm$ 0.06	0.08 $\pm$ 0.10	0.07 $\pm$ 0.13	0.07 $\pm$ 0.12
0	0.04 $\pm$ 0.14	0.05 $\pm$ 0.11	0.03 $\pm$ 0.07	0.05 $\pm$ 0.12	0.04 $\pm$ 0.12	0.05 $\pm$ 0.12
10	0.04 $\pm$ 0.09	0.03 $\pm$ 0.09	0.02 $\pm$ 0.08	0.04 $\pm$ 0.08	0.02 $\pm$ 0.09	0.03 $\pm$ 0.10
20	-0.01 $\pm$ 0.07	0 $\pm$ 0.06	0 $\pm$ 0.05	0.01 $\pm$ 0.05	0.01 $\pm$ 0.05	0.01 $\pm$ 0.06
30	0 $\pm$ 0.07	-0.02 $\pm$ 0.04	-0.02 $\pm$ 0.03	0.01 $\pm$ 0.04	0 $\pm$ 0.05	0.02 $\pm$ 0.04
40	-0.01 $\pm$ 0.04	-0.01 $\pm$ 0.04	0 $\pm$ 0.03	0.03 $\pm$ 0.04	-0.01 $\pm$ 0.04	-0.01 $\pm$ 0.04
BA			0.06 $\pm$ 0,08			
U <sub>high</sub>			0.07 $\pm$ 0,10			
U <sub>mid</sub>			0.05 $\pm$ 0,09			
U <sub>low</sub>			0.06 $\pm$ 0,10			

BA, base-apex recording; E/E<sub>10/20/30</sub>, intra-esophageal recording with interelectrode distance of 10, 20 or 30 cm; E/S<sub>high/mid/low</sub>, combined esophageal-surface recording with surface electrode positioned high, mid or low; U, unipolar recording

Table 2: Mean amplitude of  $P_2$  for different recording configurations at different recording depths. Within each column, values marked with \* are significantly larger than values without superscript but not significantly larger than values marked with °.

Catheter depth	Recording configuration					
	E/E <sub>30</sub>	E/E <sub>20</sub>	E/E <sub>10</sub>	E/S <sub>high</sub>	E/S <sub>mid</sub>	E/S <sub>low</sub>
<b>-80</b>	-	-	-	0.25 ± 0.07	0.29 ± 0.09	0.27 ± 0.07
<b>-70</b>	-	-	-	0.26 ± 0.05	0.29 ± 0.07	0.27 ± 0.06
<b>-60</b>	-	-	-	0.26 ± 0.06	0.29 ± 0.06	0.26 ± 0.07
<b>-50</b>	-0.02 ± 0.04	-	-	0.26 ± 0.07	0.28 ± 0.07	0.26 ± 0.06
<b>-40</b>	-0.07 ± 0.04	-0.02 ± 0.03	-	0.26 ± 0.07	0.28 ± 0.07	0.27 ± 0.07
<b>-30</b>	-0.14 ± 0.06	-0.08 ± 0.04	-0.02 ± 0.06	0.27 ± 0.07	0.29 ± 0.07	0.27 ± 0.06
<b>-20</b>	-0.11 ± 0.15	-0.08 ± 0.11	-0.05 ± 0.05	0.29 ± 0.06	0.32 ± 0.08	0.29 ± 0.07
<b>-10</b>	0.10 ± 0.21	-0.07 ± 0.14	-0.09 ± 0.05	0.34 ± 0.08	0.35 ± 0.10	0.34 ± 0.08
<b>0</b>	0.29 ± 0.12°	0.12 ± 0.20	0.03 ± 0.15	0.39 ± 0.10°	0.42 ± 0.09°	0.38 ± 0.09°
<b>10</b>	0.31 ± 0.09*	0.3 ± 0.11*	0.17 ± 0.13*	0.4 ± 0.09*	0.42 ± 0.09*	0.41 ± 0.09*
<b>20</b>	0.25 ± 0.10°	0.22 ± 0.09°	0.17 ± 0.08*	0.32 ± 0.11	0.36 ± 0.12	0.34 ± 0.12
<b>30</b>	0.15 ± 0.07	0.14 ± 0.05	0.10 ± 0.04°	0.21 ± 0.07	0.24 ± 0.10	0.23 ± 0.09
<b>40</b>	0.08 ± 0.02	0.07 ± 0.02	0.05 ± 0.01°	0.17 ± 0.04	0.18 ± 0.06	0.17 ± 0.09
<b>BA</b>				0.19 ± 0.05		
<b>U<sub>high</sub></b>				0.28 ± 0.15		
<b>U<sub>mid</sub></b>				0.34 ± 0.12		
<b>U<sub>low</sub></b>				0.31 ± 0.09		

BA, base-apex recording; E/E<sub>10/20/30</sub>, intra-esophageal recording with interelectrode distance of 10, 20 or 30 cm; E/S<sub>high/mid/low</sub>, combined esophageal-surface recording with surface electrode positioned high, mid or low; U, unipolar recording

Table 3: Mean amplitude of Q wave for different recording configurations at different recording depths (average $\pm$ SD).

Catheter depth	Recording configuration					
	E/E <sub>30</sub>	E/E <sub>20</sub>	E/E <sub>10</sub>	E/S <sub>high</sub>	E/S <sub>mid</sub>	E/S <sub>low</sub>
<b>-80</b>	-	-	-	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0
<b>-70</b>	-	-	-	-0.04 $\pm$ 0.14	-0.07 $\pm$ 0.27	-0.07 $\pm$ 0.28
<b>-60</b>	-	-	-	-0.03 $\pm$ 0.13	-0.05 $\pm$ 0.22	-0.07 $\pm$ 0.29
<b>-50</b>	-0.04 $\pm$ 0.02	-	-	-0.03 $\pm$ 0.12	-0.05 $\pm$ 0.22	-0.07 $\pm$ 0.29
<b>-40</b>	-0.05 $\pm$ 0.03	-0.03 $\pm$ 0.02	-	-0.03 $\pm$ 0.13	-0.05 $\pm$ 0.21	-0.04 $\pm$ 0.20
<b>-30</b>	-0.08 $\pm$ 0.03	-0.05 $\pm$ 0.03	-0.05 $\pm$ 0.02	-0.04 $\pm$ 0.12	-0.05 $\pm$ 0.22	-0.07 $\pm$ 0.30
<b>-20</b>	-0.09 $\pm$ 0.04	-0.07 $\pm$ 0.02	-0.04 $\pm$ 0.01	-0.03 $\pm$ 0.12	-0.04 $\pm$ 0.19	-0.06 $\pm$ 0.27
<b>-10</b>	-0.05 $\pm$ 0.06	-0.07 $\pm$ 0.06	-0.04 $\pm$ 0.02	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0
<b>0</b>	-0.03 $\pm$ 0.10	-0.03 $\pm$ 0.03	-0.02 $\pm$ 0.03	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0
<b>10</b>	0 $\pm$ 0	0 $\pm$ 0.01	-0.02 $\pm$ 0.05	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0
<b>20</b>	0 $\pm$ 0	0 $\pm$ 0	-0.02 $\pm$ 0.07	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0
<b>30</b>	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0.01	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0
<b>40</b>	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0	-0.06 $\pm$ 0.12	0 $\pm$ 0	0 $\pm$ 0
<b>BA</b>				-0,07 $\pm$ 0,32		
<b>U<sub>high</sub></b>				-0,06 $\pm$ 0,14		
<b>U<sub>mid</sub></b>				-0,12 $\pm$ 0,31		
<b>U<sub>low</sub></b>				-0,2 $\pm$ 0,49		

BA, base-apex recording; E/E<sub>10/20/30</sub>, intra-esophageal recording with interelectrode distance of 10, 20 or 30 cm; E/S<sub>high/mid/low</sub>, combined esophageal-surface recording with surface electrode positioned high, mid or low; U, unipolar recording

Table 4: Mean amplitude of R wave for different recording configurations at different recording depths (average $\pm$ SD).

Catheter depth	Recording configuration					
	E/E <sub>30</sub>	E/E <sub>20</sub>	E/E <sub>10</sub>	E/S <sub>high</sub>	E/S <sub>mid</sub>	E/S <sub>low</sub>
<b>-80</b>	-	-	-	0.25 $\pm$ 0.14	0.30 $\pm$ 0.18	0.30 $\pm$ 0.15
<b>-70</b>	-	-	-	0.26 $\pm$ 0.15	0.28 $\pm$ 0.16	0.28 $\pm$ 0.17
<b>-60</b>	-	-	-	0.23 $\pm$ 0.15	0.27 $\pm$ 0.17	0.27 $\pm$ 0.15
<b>-50</b>	0.28 $\pm$ 0.11	-	-	0.24 $\pm$ 0.14	0.24 $\pm$ 0.16	0.27 $\pm$ 0.17
<b>-40</b>	0.47 $\pm$ 0.19	0.23 $\pm$ 0.11	-	0.24 $\pm$ 0.17	0.26 $\pm$ 0.18	0.25 $\pm$ 0.17
<b>-30</b>	0.66 $\pm$ 0.13	0.48 $\pm$ 0.17	0.27 $\pm$ 0.08	0.23 $\pm$ 0.16	0.26 $\pm$ 0.18	0.26 $\pm$ 0.18
<b>-20</b>	0.66 $\pm$ 0.16	0.55 $\pm$ 0.13	0.36 $\pm$ 0.08	0.23 $\pm$ 0.16	0.27 $\pm$ 0.18	0.26 $\pm$ 0.16
<b>-10</b>	0.35 $\pm$ 0.25	0.41 $\pm$ 0.18	0.27 $\pm$ 0.09	0.22 $\pm$ 0.12	0.26 $\pm$ 0.14	0.27 $\pm$ 0.16
<b>0</b>	0.21 $\pm$ 0.12	0.20 $\pm$ 0.13	0.19 $\pm$ 0.14	0.22 $\pm$ 0.11	0.26 $\pm$ 0.13	0.28 $\pm$ 0.15
<b>10</b>	0.21 $\pm$ 0.08	0.15 $\pm$ 0.06	0.10 $\pm$ 0.07	0.22 $\pm$ 0.08	0.26 $\pm$ 0.11	0.29 $\pm$ 0.13
<b>20</b>	0.20 $\pm$ 0.08	0.17 $\pm$ 0.05	0.09 $\pm$ 0.03	0.18 $\pm$ 0.07	0.23 $\pm$ 0.11	0.25 $\pm$ 0.12
<b>30</b>	0.16 $\pm$ 0.08	0.15 $\pm$ 0.05	0.10 $\pm$ 0.04	0.13 $\pm$ 0.07	0.16 $\pm$ 0.08	0.20 $\pm$ 0.10
<b>40</b>	0.12 $\pm$ 0.04	0.11 $\pm$ 0.06	0.09 $\pm$ 0.03	0.13 $\pm$ 0.10	0.09 $\pm$ 0.05	0.09 $\pm$ 0.04
<b>BA</b>				0.28 $\pm$ 0.13		
<b>U<sub>high</sub></b>				0.39 $\pm$ 0.20		
<b>U<sub>mid</sub></b>				0.36 $\pm$ 0.22		
<b>U<sub>low</sub></b>				0.28 $\pm$ 0.21		

BA, base-apex recording; E/E<sub>10/20/30</sub>, intra-esophageal recording with interelectrode distance of 10, 20 or 30 cm; E/S<sub>high/mid/low</sub>, combined esophageal-surface recording with surface electrode positioned high, mid or low; U, unipolar recording

Table 5: Mean amplitude of S wave for different recording configurations at different recording depths (average $\pm$ SD).

Catheter depth	Recording configuration					
	E/E <sub>30</sub>	E/E <sub>20</sub>	E/E <sub>10</sub>	E/S <sub>high</sub>	E/S <sub>mid</sub>	E/S <sub>low</sub>
<b>-80</b>	-	-	-	-0.54 $\pm$ 0.28	-0.73 $\pm$ 0.28	-0.94 $\pm$ 0.27
<b>-70</b>	-	-	-	-0.45 $\pm$ 0.25	-0.64 $\pm$ 0.31	-0.88 $\pm$ 0.37
<b>-60</b>	-	-	-	-0.47 $\pm$ 0.23	-0.68 $\pm$ 0.30	-0.94 $\pm$ 0.37
<b>-50</b>	0 $\pm$ 0	-	-	-0.46 $\pm$ 0.22	-0.66 $\pm$ 0.30	-0.95 $\pm$ 0.37
<b>-40</b>	0 $\pm$ 0	0 $\pm$ 0	-	-0.48 $\pm$ 0.24	-0.65 $\pm$ 0.33	-0.95 $\pm$ 0.32
<b>-30</b>	0 $\pm$ 0	0 $\pm$ 0	0 $\pm$ 0	-0.48 $\pm$ 0.24	-0.67 $\pm$ 0.33	-0.97 $\pm$ 0.38
<b>-20</b>	0 $\pm$ 0.02	-0.01 $\pm$ 0.02	0 $\pm$ 0	-0.59 $\pm$ 0.34	-0.78 $\pm$ 0.40	-1.05 $\pm$ 0.48
<b>-10</b>	-0.26 $\pm$ 0.29	-0.03 $\pm$ 0.06	-0.01 $\pm$ 0.01	-0.85 $\pm$ 0.37	-1.06 $\pm$ 0.40	-1.36 $\pm$ 0.46
<b>0</b>	-0.75 $\pm$ 0.51	-0.35 $\pm$ 0.34	-0.09 $\pm$ 0.11	-1.06 $\pm$ 0.38	-1.32 $\pm$ 0.43	-1.56 $\pm$ 0.43
<b>10</b>	-1.15 $\pm$ 0.32	-0.76 $\pm$ 0.35	-0.30 $\pm$ 0.21	-1.11 $\pm$ 0.24	-1.29 $\pm$ 0.30	-1.59 $\pm$ 0.31
<b>20</b>	-1.12 $\pm$ 0.19	-0.95 $\pm$ 0.17	-0.46 $\pm$ 0.20	-0.92 $\pm$ 0.24	-1.12 $\pm$ 0.26	-1.46 $\pm$ 0.31
<b>30</b>	-0.86 $\pm$ 0.23	-0.87 $\pm$ 0.19	-0.53 $\pm$ 0.13	-0.57 $\pm$ 0.23	-0.82 $\pm$ 0.25	-1.09 $\pm$ 0.32
<b>40</b>	-0.56 $\pm$ 0.12	-0.56 $\pm$ 0.21	-0.47 $\pm$ 0.13	-0.28 $\pm$ 0.37	-0.57 $\pm$ 0.34	-0.76 $\pm$ 0.37
<b>BA</b>			-1.23 $\pm$ 0.42			
<b>U<sub>high</sub></b>			-0.21 $\pm$ 0.16			
<b>U<sub>mid</sub></b>			-0.45 $\pm$ 0.38			
<b>U<sub>low</sub></b>			-0.75 $\pm$ 0.48			

BA, base-apex recording; E/E<sub>10/20/30</sub>, intra-esophageal recording with interelectrode distance of 10, 20 or 30 cm; E/S<sub>high/mid/low</sub>, combined esophageal-surface recording with surface electrode positioned high, mid or low; U, unipolar recording

Table 6: Mean amplitude of  $T_1$  wave for different recording configurations at different recording depths (average $\pm$ SD).

Catheter depth	Recording configuration					
	E/E <sub>30</sub>	E/E <sub>20</sub>	E/E <sub>10</sub>	E/S <sub>high</sub>	E/S <sub>mid</sub>	E/S <sub>low</sub>
<b>-80</b>	-	-	-	-0.10 $\pm$ 0.06	-0.17 $\pm$ 0.09	-0.30 $\pm$ 0.15
<b>-70</b>	-	-	-	-0.13 $\pm$ 0.08	-0.21 $\pm$ 0.12	-0.33 $\pm$ 0.19
<b>-60</b>	-	-	-	-0.11 $\pm$ 0.11	-0.19 $\pm$ 0.15	-0.31 $\pm$ 0.16
<b>-50</b>	0.01 $\pm$ 0.05	-	-	-0.14 $\pm$ 0.10	-0.17 $\pm$ 0.17	-0.31 $\pm$ 0.17
<b>-40</b>	0.02 $\pm$ 0.06	0 $\pm$ 0.04	-	-0.15 $\pm$ 0.07	-0.21 $\pm$ 0.10	-0.31 $\pm$ 0.13
<b>-30</b>	0.05 $\pm$ 0.10	0.02 $\pm$ 0.09	-0.01 $\pm$ 0.05	-0.13 $\pm$ 0.09	-0.21 $\pm$ 0.10	-0.31 $\pm$ 0.15
<b>-20</b>	0.06 $\pm$ 0.11	0.03 $\pm$ 0.07	0.02 $\pm$ 0.05	-0.15 $\pm$ 0.07	-0.23 $\pm$ 0.12	-0.34 $\pm$ 0.15
<b>-10</b>	0.01 $\pm$ 0.13	0.05 $\pm$ 0.11	0.03 $\pm$ 0.06	-0.12 $\pm$ 0.18	-0.21 $\pm$ 0.20	-0.35 $\pm$ 0.19
<b>0</b>	-0.08 $\pm$ 0.10	-0.01 $\pm$ 0.09	0.02 $\pm$ 0.06	-0.20 $\pm$ 0.11	-0.28 $\pm$ 0.14	-0.38 $\pm$ 0.18
<b>10</b>	-0.17 $\pm$ 0.14	-0.14 $\pm$ 0.10	-0.04 $\pm$ 0.05	-0.24 $\pm$ 0.11	-0.31 $\pm$ 0.19	-0.42 $\pm$ 0.17
<b>20</b>	-0.23 $\pm$ 0.10	-0.18 $\pm$ 0.08	-0.08 $\pm$ 0.06	-0.24 $\pm$ 0.10	-0.34 $\pm$ 0.15	-0.45 $\pm$ 0.21
<b>30</b>	-0.17 $\pm$ 0.09	-0.17 $\pm$ 0.07	-0.09 $\pm$ 0.06	-0.17 $\pm$ 0.08	-0.27 $\pm$ 0.10	-0.37 $\pm$ 0.16
<b>40</b>	-0.14 $\pm$ 0.07	-0.10 $\pm$ 0.07	-0.09 $\pm$ 0.04	-0.11 $\pm$ 0.05	-0.23 $\pm$ 0.13	-0.30 $\pm$ 0.16
<b>BA</b>				-0.50 $\pm$ 0.19		
<b>U<sub>high</sub></b>				0.04 $\pm$ 0.13		
<b>U<sub>mid</sub></b>				-0.09 $\pm$ 0.21		
<b>U<sub>low</sub></b>				-0.27 $\pm$ 0.19		

BA, base-apex recording; E/E<sub>10/20/30</sub>, intra-esophageal recording with interelectrode distance of 10, 20 or 30 cm; E/S<sub>high/mid/low</sub>, combined esophageal-surface recording with surface electrode positioned high, mid or low; U, unipolar recording

Table 7: Mean amplitude of T<sub>2</sub> wave for different recording configurations at different recording depths (average±SD).

Catheter depth	Recording configuration					
	E/E <sub>30</sub>	E/E <sub>20</sub>	E/E <sub>10</sub>	E/S <sub>high</sub>	E/S <sub>mid</sub>	E/S <sub>low</sub>
<b>-80</b>	-	-	-	0.12 ± 0.06	0.12 ± 0.06	0.13 ± 0.09
<b>-70</b>	-	-	-	0.12 ± 0.07	0.13 ± 0.07	0.14 ± 0.09
<b>-60</b>	-	-	-	0.10 ± 0.07	0.11 ± 0.07	0.13 ± 0.08
<b>-50</b>	-0.03 ± 0.01	-	-	0.11 ± 0.07	0.12 ± 0.08	0.14 ± 0.10
<b>-40</b>	-0.05 ± 0.02	-0.02 ± 0.02	-	0.12 ± 0.08	0.13 ± 0.08	0.14 ± 0.08
<b>-30</b>	-0.04 ± 0.02	-0.04 ± 0.02	-	0.11 ± 0.08	0.15 ± 0.10	0.16 ± 0.09
<b>-20</b>	-0.02 ± 0.01	-0.04 ± 0.01	-0.01 ± 0.02	0.13 ± 0.08	0.15 ± 0.09	0.18 ± 0.12
<b>-10</b>	0.11 ± 0.07	0.04 ± 0.06	-	0.16 ± 0.09	0.17 ± 0.10	0.21 ± 0.15
<b>0</b>	0.15 ± 0.07	0.10 ± 0.05	0.03 ± 0.04	0.16 ± 0.09	0.17 ± 0.10	0.20 ± 0.12
<b>10</b>	0.12 ± 0.06	0.10 ± 0.05	0.05 ± 0.04	0.12 ± 0.06	0.13 ± 0.08	0.15 ± 0.09
<b>20</b>	0.12 ± 0.08	0.09 ± 0.05	0.05 ± 0.03	0.07 ± 0.04	0.09 ± 0.06	0.11 ± 0.07
<b>30</b>	0.09 ± 0.05	0.08 ± 0.04	0.05 ± 0.02	0.05 ± 0.03	0.05 ± 0.04	0.07 ± 0.04
<b>40</b>	0.06 ± 0.03	0.05 ± 0.03	0.05 ± 0.04	0.06 ± 0.04	0.10 ± 0.05	0.05 ± 0.03
<b>BA</b>				0.14 ± 0.06		
<b>U<sub>high</sub></b>				0.14 ± 0.07		
<b>U<sub>mid</sub></b>				0.08 ± 0.06		
<b>U<sub>low</sub></b>				0.15 ± 0.08		

BA, base-apex recording; E/E<sub>10/20/30</sub>, intra-esophageal recording with interelectrode distance of 10, 20 or 30 cm; E/S<sub>high/mid/low</sub>, combined esophageal-surface recording with surface electrode positioned high, mid or low; U, unipolar recording

Table 8: Mean amplitude of  $P_{\text{magn}}/QRS_{\text{magn}}$  ratio for different recording configurations at different recording depths. Within each column, values marked with \* are significantly larger than values without superscript but not significantly larger than values marked with °.

catheter depth	recording configuration					
	E/E <sub>30</sub>	E/E <sub>20</sub>	E/E <sub>10</sub>	E/S <sub>high</sub>	E/S <sub>mid</sub>	E/S <sub>low</sub>
<b>-80</b>	-	-	-	0.38 ± 0.16	0.34 ± 0.16	0.24 ± 0.10
<b>-70</b>	-	-	-	0.44 ± 0.21	0.35 ± 0.17	0.26 ± 0.10
<b>-60</b>	-	-	-	0.43 ± 0.17	0.34 ± 0.14	0.24 ± 0.10
<b>-50</b>	0.20 ± 0.11	-	-	0.42 ± 0.2	0.35 ± 0.15	0.24 ± 0.10
<b>-40</b>	0.22 ± 0.10	0.22 ± 0.11	-	0.42 ± 0.17	0.37 ± 0.21	0.25 ± 0.12
<b>-30</b>	0.23 ± 0.10	0.20 ± 0.08	0.17 ± 0.08	0.43 ± 0.15	0.37 ± 0.17	0.25 ± 0.11
<b>-20</b>	0.31 ± 0.15	0.26 ± 0.16	0.22 ± 0.10	0.45 ± 0.25	0.37 ± 0.22	0.26 ± 0.11
<b>-10</b>	0.44 ± 0.15*	0.48 ± 0.20°	0.54 ± 0.43°	0.39 ± 0.19	0.32 ± 0.15	0.24 ± 0.08
<b>0</b>	0.42 ± 0.21°	0.59 ± 0.30*	0.61 ± 0.27°	0.36 ± 0.11	0.31 ± 0.12	0.24 ± 0.07
<b>10</b>	0.26 ± 0.06	0.42 ± 0.20°	0.66 ± 0.44*	0.32 ± 0.09	0.31 ± 0.10	0.24 ± 0.07
<b>20</b>	0.21 ± 0.07	0.22 ± 0.09	0.40 ± 0.30	0.31 ± 0.10	0.28 ± 0.10	0.21 ± 0.07
<b>30</b>	0.17 ± 0.06	0.16 ± 0.05	0.18 ± 0.07	0.36 ± 0.20	0.28 ± 0.11	0.20 ± 0.11
<b>40</b>	0.15 ± 0.06	0.13 ± 0.04	0.12 ± 0.04	0.40 ± 0.24	0.37 ± 0.17	0.25 ± 0.14
<b>BA</b>			0.14 ± 0.04			
<b>U<sub>high</sub></b>			0.61 ± 0.35			
<b>U<sub>mid</sub></b>			0.49 ± 0.30			
<b>U<sub>low</sub></b>			0.30 ± 0.13			

BA, base-apex recording; E/E<sub>10/20/30</sub>, intra-esophageal recording with interelectrode distance of 10, 20 or 30 cm; E/S<sub>high/mid/low</sub>, combined esophageal-surface recording with surface electrode positioned high, mid or low; U, unipolar recording

## FOOTNOTES

<sup>a</sup>Cardio Companion, SurgiVet, Smiths Medical, London, England

<sup>b</sup>Televet 100®, Kruuse, Marslev, Denmark

<sup>c</sup>K. Engel, Engel Engineering Services GmbH, Offenbach am Main, Germany

<sup>d</sup>Mingograf 410 System, Siemens, Selna, Sweden

<sup>e</sup>SPSS Statistics 17.0, Rel. 17.0.1. 2008, SPSS Inc, Chicago, IL

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## CHAPTER 6

# INTRA-ATRIAL ELECTROCARDIOGRAPHY IN HORSES



# DETERMINATION OF ATRIAL FIBRILLATION CYCLE LENGTH IN HORSES AND ITS ROLE IN PREDICTION OF MAINTENANCE OF SINUS RHYTHM FOLLOWING TRANSVENOUS ELECTRICAL CARADIOVERSION

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maintenance of sinus rhythm following transvenous electrical cardioversion. In  
preparation.

## SUMMARY

The purpose of this study was to describe a new, simplified technique to record intra-atrial electrograms in horses with atrial fibrillation (AF) and to identify risk factors predicting AF recurrence after successful treatment with transvenous electrical cardioversion (TVEC). In 21 horses with AF a clinical examination, base-apex ECG, full echocardiographic examination and intra-atrial electrogram were performed prior to treatment with TVEC. In all horses a high-quality intra-atrial electrogram could be recorded and allowed accurate determination of AFCL. Identified risk factors potentially useful for the prediction of AF recurrence were left atrial size, mean AFCL, ratio of the 5<sup>th</sup> percentile AFCL (p5AFCL) and left atrial size, and ratio of p5AFCL and left atrial size relative to aortic diameter. Significance of the identified risk factors remained rather low, indicating that besides electrical remodeling and atrial size, other factors might be important for predicting the risk of AF recurrence.

## INTRODUCTION

With a prevalence of about 2.5%<sup>1</sup> and an important impact on athletic performance, atrial fibrillation (AF) represents the most important supraventricular dysrhythmia in horses. AF can be treated pharmacologically using quinidine sulphate, a class IA drug, but treatment of choice is currently transvenous electrical cardioversion (TVEC).<sup>2-4</sup> Success rate of TVEC is higher than that reported for pharmacological treatment.<sup>4,5</sup> Recurrence rate after pharmacological treatment is reported to be between 29% and 40%.<sup>5,6</sup> Data for the recurrence rate after TVEC are currently lacking, but recurrence rate is probably independent of the treatment technique and therefore is likely to be similar to that reported for pharmacological conversion of AF.<sup>7</sup> The variation in the reported recurrence rate is likely to be explained by differences in breed of the treated horses. Higher recurrence rates have been reported for warmblood horses compared with Thoroughbreds, which might be related to atrial size and AF duration. Large atria are a known risk factor promoting AF.<sup>8,9</sup>

Objective criteria that allow prediction of AF recurrence after successful TVEC are currently unavailable in horses. In two studies on AF in horses, it was noted that recurrences became more frequent when AF was present for a longer period prior to treatment.<sup>6,10</sup> In human medicine atrial size, duration of AF and atrial fibrillation cycle length (AFCL) are parameters used to predict recurrence of AF after successful treatment.<sup>11,12</sup> AFCL is an index of atrial effective refractory period (AERP), an electrophysiological parameter strongly related to AF susceptibility.<sup>13-15</sup> During AF, electrical remodeling by AERP shortening leads to increased AF sustainability.<sup>13,14</sup> After restoration of sinus rhythm, reverse electrical remodeling to pre-AF levels takes time, during which the atria are vulnerable to early AF recurrence.<sup>13</sup>

Currently there is no simple technique in horses to record an intra-atrial electrogram and determine AFCL. Two previous studies in horses with naturally occurring AF used a pacemaker and pacemaker programmer to record intra-atrial electrograms,<sup>16,17</sup> but this method requires the availability of expensive equipment. The purpose of this study was to describe a simple method to record intra-atrial electrograms in horses and to identify possible factors predicting AF recurrence following successful TVEC.

## MATERIALS AND METHODS

### STUDY POPULATION

Horses referred to the Department of Large Animal Internal Medicine for treatment of AF were included in this study. Mean age, body weight and height at the withers were recorded. All horses were treated by transvenous electrical cardioversion (TVEC). Inclusion criteria were the availability of a clinical examination, a base-apex ECG recording and a full echocardiographic examination, and successful restoration of sinus rhythm. Horses with significant valvular regurgitation were excluded from the study.

### RECORDED DATA

AF duration was estimated based upon history and previous examinations. The two-dimensional ultrasonographic measurements from the left (L) and right (R) parasternal long axis view included left atrial (LA) internal diameter during ventricular systole. From a right parasternal short axis (<sub>sa</sub>) view, internal diameters of LA (LA<sub>sa</sub>) and aorta (Ao) during ventricular systole were obtained.

In the standing, non-sedated horse a 14F introducer sheath<sup>a</sup> was inserted in the lower half of the jugular vein. Through this sheath two cardioversion catheters<sup>b</sup> and one bipolar sensing/pacing electrode<sup>c</sup> were inserted under echocardiographic guidance. The sensing/pacing catheter was positioned in the right atrium and a bipolar intra-atrial electrogram was digitally recorded with a modified<sup>d</sup> ECG recording device<sup>e</sup> during 15 minutes while cardioversion catheters were positioned in the left pulmonary artery and the right atrium. During off-line analysis, the time interval between consecutive intra-atrial depolarizations, which is the AFCL, was manually measured over 500 depolarizations using dedicated software<sup>f</sup> (Fig. 1). Paper speed and amplitude were 50 mm/s and 10 mm/mV, respectively.

After recovery from TVEC, clinical status was followed and surface electrocardiograms were recorded on days 1, 2, 7 and 42 after cardioversion. Mean follow-up period was 392±252 days (range 105 to 1058 days).

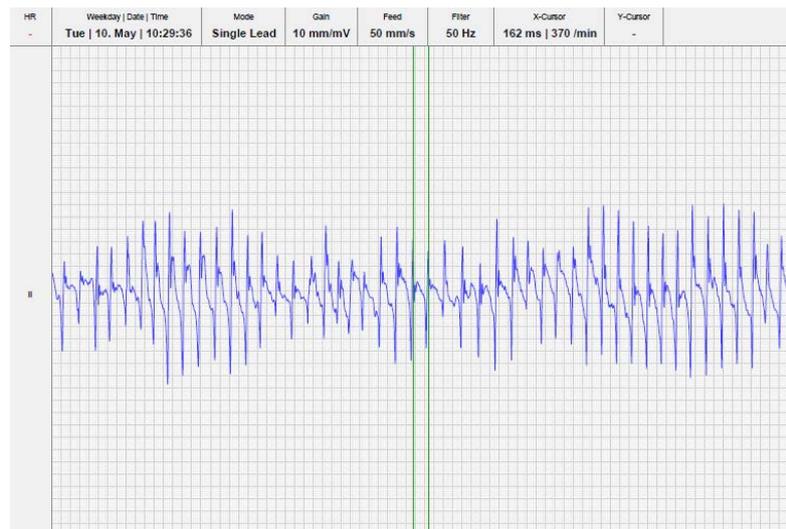


Figure 1: Intra-atrial electrogram from a horse with atrial fibrillation. The atrial fibrillation cycle length is the time (milliseconds) between two successive atrial depolarizations. The current measurement indicates an AFCL of 162ms which corresponds to a fibrillation rate of 370/min.

## STATISTICAL ANALYSIS

All variables are reported as mean±standard deviation. Independent samples T-tests were performed on age, body weight, height, estimated duration of AF, LLA, RLA, LA<sub>sa</sub>/Ao, mean AFCL, p5AFCL, ratio p5AFCL/LLA, ratio p5AFCL/RLA and ratio p5AFCL/(LA<sub>sa</sub>/Ao) between horses maintaining sinus rhythm and those who suffered from AF recurrence. For all comparisons, values of  $p < 0.05$  were considered significant. Cox's proportional hazards model was used to identify prognostic factors to predict AF recurrence and to evaluate univariate relative risks as  $\exp(\text{regression coefficient} \times (\text{factor difference}))$ . A univariate Cox's regression model was adapted to the data for each parameter which had a high score ( $p \leq 0.10$ ), before any factor was entered into the model.

## RESULTS

Twenty-one horses (8 geldings, 7 mares, 6 stallions; 19 warmbloods, 1 Friesian, 1 Anglo-arabian) were presented with AF and were successfully cardioverted by TVEC. All horses met the criteria for inclusion and were used in this study. In all horses, high-quality intra-atrial electrograms could be recorded and allowed accurate determination of AFCL.

Baseline parameters determined in all horses are presented in Table 1.

Table 1: Baseline characteristics (mean±SD) of the horses remaining in sinus rhythm and those suffering from AF recurrence after transvenous electrical cardioversion.

	<b>mSR</b>	<b>rAF</b>	<b>P value</b>
age (years)	10.5±2.8	9.8±4.5	0.659
body weight (kg)	575±23	602±64	0.322
height (cm)	170±6	170±10	0.971
estimated AF duration (months)	5.7±4.4	11.8±17.2	0.233
<b>LLA (cm)</b>	12.4±0.9	13.2±0.6	<b>0.006</b>
<b>RLA (cm)</b>	11.7±0.7	12.7±0.6	<b>0.033</b>
LA <sub>sa</sub> /Ao	1.13±0.12	1.22±0.08	0.068
mean AFCL (ms)	168±15	151±24	0.073
p5AFCL (ms)	142±15	132±22	0.244
<b>p5AFCL/LLA (ms/cm)</b>	11.6±1.6	10.1±1.6	<b>0.049</b>
<b>p5AFCL/RLA (ms/cm)</b>	12.2±1.7	10.5±1.6	<b>0.036</b>
<b>p5AFCL/(LA/Ao) (ms)</b>	127.7±22.7	108.2±11.5	<b>0.037</b>

AFCL: atrial fibrillation cycle length; Ao: aortic diameter; cm: centimeter; LLA: left atrial diameter measured from the left parasternal long axis view; LA<sub>sa</sub>: left atrial internal diameter measured from the right parasternal short axis view; mSR: maintenance of sinus rhythm; rAF: recurrence of atrial fibrillation; RLA: left atrial diameter measured from the right parasternal long axis view; p5: 5<sup>th</sup> percentile

Values are shown for horses remaining in sinus rhythm (n=13; 62%) versus horses suffering from AF recurrence (n=8; 38%). There was no significant difference for mean age, body weight, height at the withers, estimated duration of AF, LA<sub>sa</sub>/Ao, mean AFCL and p5AFCL between horses who remained in sinus rhythm and those suffering from AF recurrence. LLA and RLA were significantly larger in horses suffering from AF

recurrence. The ratios of p5AFCL/LLA, p5AFCL/RLA and p5AFCL/(LA<sub>sa</sub>/Ao) were significantly lower in horses suffering from AF recurrence. Individual results of p5AFCL/LLA as a function of LLA of horses with AF recurrence and those remaining in sinus rhythm are shown in Figure 2.

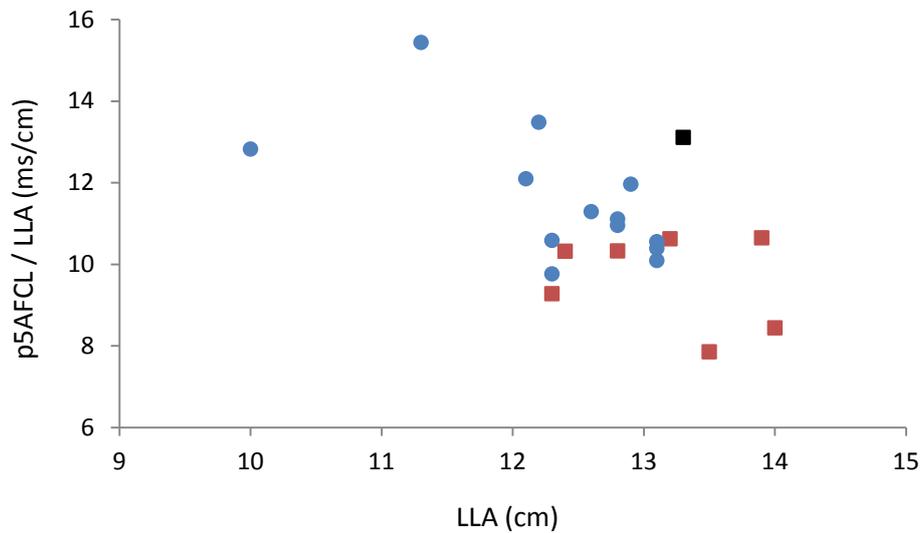


Figure 2: Scatterplot of the ratio of the 5<sup>th</sup> percentile (p5) atrial fibrillation cycle length (AFCL) and left atrial diameter (LLA) measured from the left parasternal long-axis view, as a function of LLA of horses with recurrence of atrial fibrillation (■, ■) and those remaining in sinus rhythm (•) after successful cardioversion. Black square indicates the horse with the highest p5AFCL/LLA in the recurrence of atrial fibrillation group.

There is a significant negative correlation between mean AFCL and estimated duration of AF (Spearman's rank correlation coefficient -0.602;  $p=0.004$ ). Individual results of mean AFCL as a function of estimated duration of AF are shown in Figure 3.

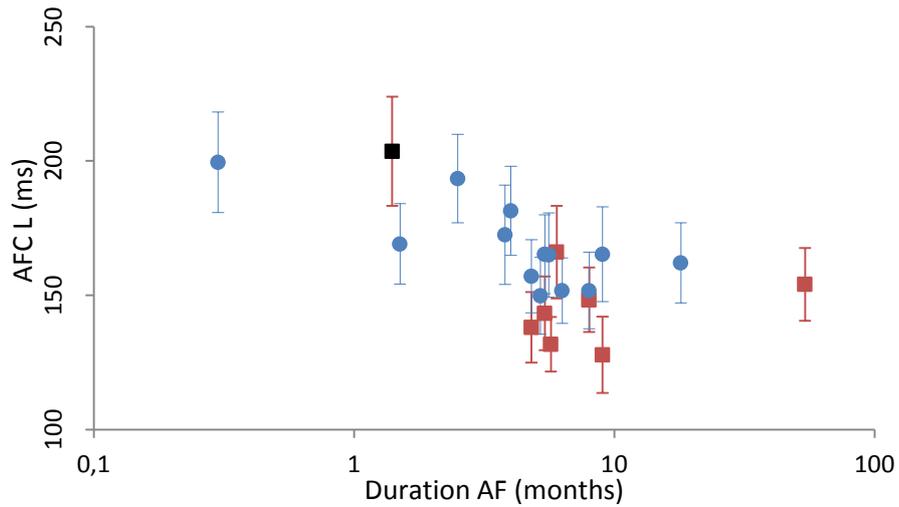


Figure 3: Scatterplot of atrial fibrillation cycle length (AFCL; ms; mean±SD) as a function of estimated atrial fibrillation duration on a logarithmic scale of horses with recurrence of atrial fibrillation (■, ■) and those remaining in sinus rhythm (•) after successful cardioversion.

One horse (■) suffered from AF recurrence despite a short estimated AF duration and long mean AFCL. In this horse, ratio of  $p5AFCL/LLA$  was highest of all horses suffering from AF recurrence.

Regression coefficients of the univariate Cox's regression models and the relative risks for AF recurrence after TVEC compared to the mSR group, based on the factor values in both groups (given in Table 1) are shown in Table 2.

Table 2: Prognostic value of several factors related to recurrence-free time after successful cardioversion in univariate Cox's regression models, and relative risk calculated from prognostic factor values, given in Table 1, for patients in recurrence of atrial fibrillation versus maintaining sinus rhythm group.

Prognostic factor	Prognostic value		Difference rAF versus mSR group	p value	Relative risk
	Regression coefficient	Standard error			
<b>LLA (cm)</b>	1.61	0.71	0.82±0.36	<b>0.024</b>	<b>3.74</b>
<b>p5AFCL/LLA (ms/cm)</b>	-0.74	0.36	1.50±0.72	<b>0.039</b>	<b>3.05</b>
<b>p5AFCL/(LA<sub>sa</sub>/Ao)</b>	-0.07	0.04	19.55±8.69	<b>0.045</b>	<b>4.01</b>
<b>mean AFCL (ms)</b>	-0.06	0.39	16.38±8.64	<b>0.049</b>	<b>2.54</b>
p5AFCL/RLA	-0.63	0.32	1.72±0.76	0.052	2.94
p5AFCL (ms)	-0.04	0.03	9.6±7.99	0.197	1.45
RLA (cm)	0.90	0.47	0.94±0.30	0.054	2.33
LA <sub>sa</sub> /Ao	1.60	7.80	0.09±0.04	0.109	2.04

AFCL: atrial fibrillation cycle length; Ao: aortic diameter; LLA: left atrial diameter measured from a left parasternal long axis view; LA<sub>sa</sub>: left atrial internal diameter measured from a right parasternal short axis view; mSR; maintenance of sinus rhythm; rAF; recurrence of AF; RLA: left atrial diameter measured from a right parasternal long axis view; p5: 5<sup>th</sup> percentile

Significant relative risks for LLA, mean AFCL, p5AFCL/LLA and p5AFCL/(LA<sub>sa</sub>/Ao) were obtained from Cox's regression models (Table 2). The larger LLA, by 0.82±0.36 cm in rAF versus mSR horses, resulted in a relative risk of 3.74 (95% confidence interval (CI) = 1.2, 11.7; p=0.024). In other words and recalculated, each cm increment in LA diameter increases the relative risk of recurrence of AF by a factor 5.0 (CI=1.2, 20). The smaller p5AFCL/LLA, by 1.50±0.72 ms/cm in rAF vs mSR, resulted in a relative risk of 3.05 (CI=1.06, 8.82). In other words, each decrement in p5AFCL/LLA ms/cm increases the relative risk of recurrence of AF by a factor 2.10 (CI = 1.04, 4.3). Similarly, the relative risks for the other two significant factors can be recalculated from Table 2 to 1.07 (CI=1.00, 1.15) per ms/cm decrement in p5AFCL / (LA<sub>sa</sub>/Ao), and 1.06 (CI=1.00, 1.12) per ms decrement in mean AFCL.

## DISCUSSION

The present study shows that intra-atrial electrograms can easily be recorded in horses and allow accurate determination of AFCL. Furthermore, our study is the first to describe criteria that allow assessment of the risk of AF recurrence in horses following electrical cardioversion. Left atrial size, mean AFCL, ratio of p5AFCL/LLA and ratio of p5AFCL/(LA<sub>sa</sub>/Ao) were identified as potential risk factors predicting AF recurrence after restoration of sinus rhythm.

In all horses high quality intra-atrial electrograms could be recorded using a right atrial temporary pacing/sensing catheter and a digital recording device.

In literature no data are available on the recurrence rate of AF after successful TVEC. Recurrence rate in our study was 38%, which is in agreement with the study of Goltz et al. who reported a recurrence rate of 40% after pharmacological treatment of AF in warmblood horses.<sup>5</sup> Recurrence rate stated by Reef et al. after pharmacological treatment of Thoroughbreds and Standardbreds was only 29%.<sup>6</sup> Horse breed is an important factor explaining this difference: warmblood horses are generally larger than Thoroughbreds or Standardbreds, have larger atria and hence are more susceptible to AF.<sup>8,9</sup> In addition, in racehorses AF is often of shorter duration because clinical signs are usually more obvious compared to warmbloods.

The inducibility and sustainability of AF depends on the ability of the atria to maintain a critical number of re-entry circuits.<sup>18</sup> Identified factors in favor of AF are large atrial size, short atrial effective refractory period (AERP) and atrial structural disease.<sup>13,14</sup> Large atria are considered a risk factor for AF induction because they promote the coexistence of multiple wavelets. In horses, there is no golden standard for determination of the most accurate LA diameter. Therefore, LA diameters from left and right parasternal views were taken into account and both were significantly larger in horses with AF recurrence. When taking the existing differences in follow-up period into account, our study shows that left atrial size is an important factor for predicting AF recurrence, with an increase in relative risk of AF recurrence by a factor 5.0 for every cm increment in left atrial diameter.

Since the length of a wavelet circulating in the atria is the product of conduction velocity and AERP, a decrease in either conduction velocity or AERP will lead to an increase in the maximum number of wavelets that can coexist in the atria.<sup>19</sup> AERP can be

determined during sinus rhythm by programmed electrical stimulation using temporary or implanted pacing devices.<sup>20,21</sup> However, during AF this technique cannot be used. AFCL and minimum AFCL (5<sup>th</sup> percentile of AFCL, p5AFCL) have been shown to be an index of AERP.<sup>15,22</sup> From reports investigating the effects of AF on atrial electrophysiology it has been concluded that AFCL and AERP shorten with maintenance of AF, and prolong progressively after medical treatment or ablation.<sup>13,23-25</sup> An experimentally induced AF model in equines showed that the shortening of AFCL occurs mainly in the first weeks after AF induction.<sup>20,21,26</sup> Our study in horses with naturally occurring AF confirmed that increasing estimated duration of AF was significantly correlated with shortening of AFCL (Fig. 3). When the differences in follow-up were taken into account, mean AFCL was found to be a significant factor in predicting AF recurrence: each ms decrement in AFCL resulted in an increase of the relative risk of AF recurrence by a factor 1.06. One horse showed AF recurrence although it had the longest mean AFCL (203 ms) of all treated horses (Fig. 3). The long AFCL might be explained by the relatively short estimated duration of AF (1.5 months), allowing less time for electrical remodeling. On the other hand, this horse had an atrial diameter of 13.3 cm. Looking at Figure 2, all horses (n=5) with an atrial diameter in excess of 13.2 cm did show AF recurrence. Naturally, multiple factors contribute to the risk for AF recurrence. Although the small number of horses in our study requires careful interpretation, Figure 2 might suggest that horses with an atrial size in excess of 13.2 cm are likely to relapse in AF, whatever their AFCL, while horses with smaller atria only show AF recurrence when their AFCL is sufficiently short.

Combining parameters of atrial electrical remodeling and morphology identified additional risk factors for AF recurrence. Each unit decrement in p5AFCL/LLA resulted in an increase of the relative risk of AF recurrence by a factor 2.10. When using an anatomical parameter which corrects for horse size in the ratio ( $LA_{sa}/Ao$ ), the relative risk of AF recurrence was increased by a factor 1.07 per unit decrement.

In human medicine, numerous studies have aimed at identifying factors predicting maintenance of sinus rhythm following cardioversion,<sup>11,12,27-29</sup> but only AF duration, left atrial size and AFCL have shown consistent value. Contrary to human medicine, our study did not identify AF duration as a significant risk factor for AF recurrence in horses. The two studies in horses which suggested that AF duration might have an influence on recurrence rate, were performed in a larger study population.<sup>6,10</sup> Including a larger

number of horses in our study might result in a significant difference between the two groups.

Significance level of all four identified parameters to predict AF recurrence was relatively low. This might indicate that other factors, besides electrical remodeling and atrial size, should be considered in determining the risk of AF recurrence. Documented additional factors potentially triggering and promoting AF are ectopic atrial foci, rotors and parameters indicating structural remodeling of the atria.<sup>30,31</sup> Changes in the distribution of the protein connexin 40, myolysis characterized by disruption of the sarcoplasmic reticulum, accumulation of glycogen and the presence of apoptosis or fibrosis have been shown in human medicine to influence the outcome of cardioversion and AF recurrence.<sup>32-34</sup> Also in horses atrial fibrosis has been associated with the development of AF.<sup>1</sup> Currently no additional information is available about the importance of these mechanisms in horses.

Our study included a number of limitations. Studies have shown that AFCL is subjected to spatial and temporal dispersion, with shortest AFCL usually measured in the left atrium.<sup>35</sup> We measured local AFCL from the right atrium only as left atrial catheterization is technically very difficult in horses. However, the purpose of this study was to evaluate a technique that is easily applicable in clinical patients.

A second limitation of our study is that baseline AERP (AERP during normal sinus rhythm) was not measured. We measured local AFCL which represents the AERP after electrical remodeling due to AF. AF duration but also individual degree of AF-induced remodeling may differ between horses. In addition, the relation between baseline AERP and AERP in the remodeled atrium may show individual differences.

Another limitation of this study was that the presence of atrial structural lesion could not be established. Preliminary results suggest that diffuse fibrosis is difficult to detect by 2D speckle tracking or tissue Doppler imaging and autopsies were not performed.

A further limitation was the relatively low number of horses included in our study. Despite this low number, four parameters were found potentially useful for prediction of AF recurrence while the analysis was univariate. A larger scale study together with multivariate analysis might result in a better prediction of AF recurrence. It is likely that some parameters mentioned in Table 2 then will reach significance level.

In a number of horses, AF duration was subjectively estimated from their history and previous examinations. As clinical signs of AF are often less obvious in warmblood

horses when compared to Thoroughbreds, a certain degree of estimation cannot be avoided.

Time for follow-up differed between horses, reducing the reliability of the results from the T-test (Table 1), and necessitating the use of Cox's regression models (Table 2). Standardizing follow-up time for all horses might reveal significant differences in additional parameters between horses maintaining sinus rhythm and those suffering from AF recurrence.

In conclusion, intra-atrial electrograms can be recorded in horses using a simple and effective method and allow accurate determination of local AFCL. Further development of the technique of intracardiac recording will allow the recognition and increased understanding of several dysrhythmias. Despite the rather small number of horses, this study shows that left atrial size and electrophysiological characteristics show potential as predictors for AF recurrence following TVEC. Pre-treatment measurement of these parameters might help to assess the risk for AF recurrence.

## FOOTNOTES

<sup>a</sup>Triport, Mansfield EP

<sup>b</sup>Custom catheter, Rhythm Technologies Inc., Irvine, CA

<sup>c</sup>Bipolar intracardiac electrode, USCI

<sup>d</sup>K. Engels, Engels Engineering Services GmbH, Offenbach an Main, Germany

<sup>e</sup>Televet 100<sup>®</sup>, Kruuse, Marslev, Denmark

<sup>f</sup>Televet 100<sup>®</sup> version 5.0.0, Kruuse, Marslev, Denmark

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# GENERAL DISCUSSION



This thesis explores new diagnostic strategies from the equine electrocardiogram and clearly shows that electrocardiography in horses can be used for more than rate and rhythm analysis alone. We believe that equine electrocardiography is currently underused and our research provides a basis for further development of different techniques. The availability of high quality, affordable and easy to use recording devices will contribute to this development and the expansion of our knowledge about the equine ECG.

Atrial fibrillation (AF) is an example of a cardiac disease where the use of ECG was mainly restricted to recordings at rest for diagnostic purposes. Our research (chapter 3) shows that exercising ECG recordings provide clinically important information and identify potential risk factors for weakness or collapse in exercising horses.

AF is the most important dysrhythmia in horses as it develops relatively easily and commonly affects athletic performance. Successful treatment can be achieved by medication or, more recently, by transvenous electrical cardioversion. The latter technique has a higher success rate and carries lower risks. When no other predisposing cardiac pathology is present, therapeutic success rate of cardioversion is high and prognosis after conversion to sinus rhythm is generally good since most horses regain their full athletic ability. In some horses sinus rhythm cannot be restored or treatment is declined because of financial constraints. It was generally believed that these horses could continue performing in less demanding disciplines and were safe to be ridden as long as no signs of exercise intolerance were present. Yet, anecdotal evidence suggested that for unknown reasons some of these horses suffered from weakness, incoordination, collapse or even sudden death during exercise. Our study is the first to report on specific dysrhythmias associated with AF in horses which might explain these clinical signs.

A first significant finding was the extremely high heart rate during exercise or episodes with increased sympathetic tone in horses with AF. Because the highest heart rates were always obtained in situations perceived as stressful by the horses, it is very likely that this AF-related tachycardia is mainly due to changes in autonomic tone. The high sympathetic tone during stress increases conduction through the AV node, decreasing concealed conduction and increasing the number of atrial impulses conducted to the ventricles. A contributing factor can be the dependence of the refractory period of the AV node on cycle length: a very short ventricular cycle length slightly reduces the AV nodal refractory period, hence enabling increased conduction to the ventricles. The

extreme heart rates could explain the reported signs of weakness, incoordination and collapse in horses with AF. Excessive tachycardia might have a negative effect on ventricular filling and cardiac output due to the short diastolic filling time, especially in the absence of atrial contraction.<sup>1</sup>

Abnormal QRS complexes which we categorized as ventricular premature depolarizations (VPDs) were present in 81% of the AF horses. In two recent studies, Barbesgaard et al. and Buhl et al. described a VPD prevalence in healthy dressage and show jumping horses of 5% and 18%, respectively.<sup>2,3</sup> A possible explanation for the high number of VPDs in our study is that not all complexes categorized as VPDs were real VPDs. Because abnormal complexes were often associated with stress and hence elevated heart rates, they could also be caused by aberrant conduction. During exercise, the refractory period of the AV node might become shorter than that of the bundle branches and result in aberrant ventricular conduction. At rest, a similar phenomenon, the Ashman phenomenon, can come into play.<sup>4</sup> In human medicine, some ECG criteria have been reported to aid in the differentiation between true ventricular ectopy and aberrant ventricular conduction in the presence of AF. A fixed coupling interval between abnormal beats and a substantial pause following the abnormal beat would rather indicate ectopy. A variable coupling interval, abnormal complexes with a right bundle branch pattern and an abnormal beat terminating a short cycle preceded by a long cycle, suggest aberrancy.<sup>5,6</sup> In addition, a mono- or diphasic QRS morphology, presence of similar abnormal beats in a previous or subsequent nonfibrillating record, absence of a long precedent cycle, undue prematurity of an abnormal complex and bigeminal rhythm all would be in favor of ectopy. A triphasic QRS morphology, an initial QRS vector identical to that of normally conducted beats and a long-short cycle sequence would suggest aberrancy.<sup>7</sup> Comparison of simultaneous surface and intracardiac recordings has allowed reevaluation of the surface ECG criteria and resulted in the development of better criteria. The diagnosis of ectopy is supported in case of left bundle branch block morphology, monophasic or diphasic right bundle branch block morphology, a compensatory cycle longer than the average cycle length of ten normally conducted beats and a short-long cycle sequence. Criteria for the diagnosis of aberrancy are triphasic right bundle branch morphology and similar initial vectors observed in several leads.<sup>8</sup> Many of these criteria are not flawless and require 12-lead ECGs to be recorded. The definitive diagnosis depends on intracardiac electrograms. Because of the

invasiveness of intracardiac ECG, Suyama et al. developed a method using RR interval scattergrams to differentiate between aberrancy or ectopy.<sup>4</sup> The functional refractory period of the AV node limits the rate with which supraventricular impulses can be conducted to the ventricles. When RR intervals were plotted in a scattergram, the functional refractory period could be seen as the lower limit of the scattered dots. RR intervals that distributed clearly below this lower limit were diagnosed as ventricular ectopies. Carotid sinus pressure has been used as another noninvasive method to differentiate aberrancy and ectopy.<sup>9</sup> Applying pressure to the carotid sinus resulted in delayed AV conduction, allowing adequate time to the intraventricular conduction system to recover, thereby terminating aberrancy. In case of true ventricular ectopy, carotid sinus pressure had no effect.

The differentiation between aberrancy and ectopy is more complicated in horses because 12-lead ECGs are not available and bundle branch block has not been described yet, hampering the application of most criteria from human medicine. Criteria that could be useful in horses are a compensatory cycle longer than the average cycle length of ten normally conducted beats and a short-long cycle sequence, potentially indicating ventricular ectopy, and a similar initial vector of the abnormal QRS complex compared to normal QRS complexes as a possible sign of aberrancy. When applied to the ECGs of horses with AF, both ectopy and aberrancy could be present. Most horses showed more than one type of altered QRS morphology. If aberrant conduction would underlie all abnormal QRS complexes in horses with AF, one morphology would be expected for all abnormal QRS complexes during exercise, and one morphology for all abnormal complexes at rest. On the other hand, Marriott and Sandler described the occurrence of multiple bundle branch block patterns, leading to different QRS morphologies, in the same patient.<sup>7</sup> The usefulness of RR interval scattergrams has not been investigated yet. It seems that separate scattergrams would have to be made for horses at rest and during exercise given the extreme heart rate ranges in horses with atrial fibrillation. When RR intervals at rest and during exercise would be plotted in the same scattergram, it would be very likely that the very short RR intervals during exercise would mask the line indicating the functional refractory period, making the differentiation between aberrancy and ectopy impossible. The technique of carotid sinus pressure application is unfeasible in horses given its location. Until now, the possibility of aberrant conduction has never been described in horses and it is currently unknown whether these

mechanisms indeed exist in horses. An electrophysiological study using intracardiac ECG recordings could allow a definitive diagnosis of abnormal complexes and help elucidating some of these questions. A multi-electrode catheter positioned in close proximity to the tricuspid valve can record electrical activity from the right atrium, the His bundle and the ventricle. The deflection of the His bundle is seen as a sharp biphasic or triphasic spike between the atrial and ventricular deflections, dividing the PR interval into an AH interval (conduction time through the AV node) and HV interval (conduction time through the His-Purkinje system). Every beat conducted from the atria to the ventricles must show a His bundle depolarization with the HV interval equal to or longer than that observed for normal conducted beats. A ventricular depolarization that is not preceded by a depolarization of the His bundle must arise within the distal His-Purkinje system and must be considered a true VPD.<sup>10</sup>

Another explanation for the high number of VPDs could be adrenergic facilitation. In all horses except one, VPDs were associated with situations that could be described as stressful. In human medicine, several studies have shown that patients with AF have an increased risk for ventricular dysrhythmias.<sup>11-13</sup> The underlying mechanisms are currently poorly understood. One possible explanation could be an increase in sympathetic nerve activity due to an increase in arterial baroreflexes instituted by AF and the irregular ventricular response.<sup>14</sup> Activation of the sympathetic nerve system also occurs in association with mental stress. From studies in human medicine it is known that psychologically stressful maneuvers increase the frequency of ventricular premature beats both in healthy subjects and in patients with underlying heart disease.<sup>15-17</sup> Lown, Verrier and co-workers have shown that aversive conditioning, anger and fear in dogs decreased the threshold for severe ventricular events in healthy animals and during acute myocardial infarction.<sup>18-20</sup>  $\beta$ -adrenergic blocking drugs were able to abolish the changes in ventricular response to diverse psychological stresses in healthy dogs, confirming the role of the sympathetic nervous system.<sup>18</sup> In normal cats, ventricular dysrhythmias were frequently observed in emotional behaviors such as restlessness and threat.<sup>21,22</sup> In healthy rats subjected to social stress, a general association between the level of cardiac sympathetic activation and the amount of rhythm disturbances was found.<sup>23</sup> In these rats, a non-social aversive event such as restraint was associated with a much lower incidence of ventricular ectopy.

From our study it seems that also in horses with AF there is an increased risk for ventricular dysrhythmias. Currently, no data are available on the influence of sympathetic stimulation on ventricular ectopy in horses. Abnormal QRS complexes occurred when horses were distressed by objects or sounds in the environment or when encouraged to gallop at maximal speed during the exercise protocol. It seems that also in horses specific emotions can trigger the occurrence of abnormal QRS complexes. The administration of a  $\beta$ -blocker to horses showing a high number of abnormal QRS complexes in association with an increase in sympathetic tone could help elucidating this question. However, the administration of  $\beta$ -blockers cannot help in the differentiation in the origin of abnormal QRS complexes in horses with AF, because  $\beta$ -blockers also slow conduction through the AV-node, potentially reducing aberrant conduction.

Horses with lone AF are considered to have normal hearts, apart from the presence of AF. However, although the influence of the sympathetic nerve system on ventricular vulnerability has also been shown in healthy animals, horses without AF do not present such a high number of abnormal QRS complexes compared to horses with lone AF. This might indicate that the ventricular myocardium of horses with lone AF has a lower threshold for the development of ventricular events. In two recent studies in human medicine, the association between AF and the increased risk for ventricular dysrhythmias was explained by electrical remodeling of the ventricles.<sup>24,25</sup> The irregular ventricular activation associated with AF resulted in repolarization changes such as prolonged  $QT_c$  intervals and increased QT dispersion, which could certainly be prodysrhythmic. Up to date, no changes in  $QT_c$  interval or QT dispersion have been reported in horses with AF. As the induced  $QT_c$  changes are probably very small (10 to 15 milliseconds in human patients),<sup>25</sup> they might have gone unnoticed in horses with AF. On the other hand AF induced ventricular electrical remodeling might not occur in horses at all. In a study on short-term pacing-induced atrial fibrillation in horses, ventricular effective refractory period remained unchanged.<sup>26</sup> The normal ventricular response (at rest) in horses with AF is in contrast to human patients and might explain the absence of ventricular remodeling.

Besides the high number of abnormal QRS complexes classified as VPDs, 33% of the horses with AF showed QRS complexes with R-on-T morphology. Our study is the first to describe the association between AF and R-on-T phenomenon in horses. R-on-T was

always associated with situations which were thought to be stressful to the horses. The exact nature of the phenomenon, whether it is supraventricular or ventricular in origin, could not be determined from the surface ECG. Simultaneous surface and intracardiac ECG recordings combined with intracardiac electrophysiological studies might help to differentiate both rhythms. Stress might be an important factor contributing to the high number of R-on-T we observed in horses with AF. Horses were submitted to a standardized lunging exercise test in a hospital environment which differed from their normal work environment. ECG recording during the horses' normal daily activities, could have resulted in a smaller number of VPDs or R-on-T. Repeating the standardized exercise test shortly after restoration of sinus rhythm could have indicated whether ventricular ectopy was a plausible mechanism. Indeed, after restoration of sinus rhythm the persistence of a high number of abnormal QRS complexes would indicate a ventricular rather than supraventricular origin, while the absence of R-on-T complexes during a repeat test would support aberrancy. However, because horses were advised to rest for several weeks to allow full recovery of their atrial contractility,<sup>27</sup> this exercise test was not repeated. In human medicine, R-on-T is considered an important risk factor for the development of ventricular tachycardia and ventricular fibrillation, with early reports mentioning that up to 75% of R-on-T episodes deteriorated to ventricular fibrillation.<sup>28,29</sup> Later work challenged the validity of the R-on-T phenomenon as an antecedent of life-threatening dysrhythmias, certainly in the absence of cardiac disease.<sup>30,31</sup> However, its presence on an ECG recording still alerts physicians and continues to be considered a trigger for malignant dysrhythmias.<sup>29,31</sup> None of our horses with AF and R-on-T developed ventricular fibrillation. This might be due to the low number of horses examined or an indication that R-on-T is supraventricular in origin, resulting from increased conduction through the AV node. In order to investigate the origin of the R-on-T complexes, we measured AFCL from the intra-atrial ECGs recorded during AF. These data were compared with the individual beat-to-beat maximal ventricular rate during the exercise test. If the maximal ventricular rate would have been much higher than the AFCL, it could not have been caused by a one on one conduction of atrial impulses (with aberrant ventricular conduction). However, as atrial and ventricular rates did not differ much conclusions upon the origin of the broad QRS complexes and R-on-T could not be drawn. A limitation of our study was that AFCL was only measured at rest in the right atrium. AFCL is not consistent throughout both atria,

but is subjective to dispersion in both time and space. In human medicine AFCL is reported to be shorter in the left compared to the right atrium.<sup>32,33</sup> In order to draw definite conclusions on the origin of the R-on-T complexes based on atrial fibrillation rate, the number of fibrillation impulses reaching the AV node should be compared to the ventricular response. This measurement is however impossible to perform in the exercising horse.

Until now, it has been suggested that horses with AF can continue to perform at lower level of exercise as long as no signs of exercise intolerance are present. However, our study demonstrated a high number of VPDs and R-on-T phenomenon associated with AF indicating that these horses are not always safe to be ridden. In horses with lone AF that are not put at rest, treatment should therefore be encouraged to restore normal sinus rhythm. In horses that cannot be treated, and as long as the origin of the abnormal QRS complexes cannot be ascertained, an exercise ECG should always be performed, to assess the occurrence of abnormal QRS complexes and especially the R-on-T phenomenon. During the recording horses should be distressed at some point since abnormal complexes seem to be linked to adrenergic stimulation. If a high number of VPDs or R-on-T are present, clients should be advised that this might be a risk factor for the development of ventricular tachydysrhythmias. If no VPDs or R-on-T complexes are observed, horses should undergo a regular follow-up of the exercise ECG. It is possible that abnormal QRS complexes are not to be found during every single exercise test.

Atypical myopathy (AM) is another example of a disease with cardiac involvement in which ECG recordings were not routinely made. Previous research only showed that dysrhythmias could be present but failed to identify other abnormalities in cases of AM.<sup>34</sup> In human and small animal medicine, electrocardiography is an indispensable technique for the diagnosis of different myocardial disease states. Currently, in horses, no electrocardiographic alterations caused by myocardial disease are described apart from dysrhythmias. Our research (chapter 4) shows that ECG recording in case of a disease with an impact on the heart contributes to the knowledge about that disease and can even help unraveling the pathophysiology.

AM is a potentially fatal disease occurring in grazing horses, especially during autumn and spring. Postmortem examinations indicate that AM not only causes degeneration of the skeletal muscles but may also affect the myocardium. Previous studies only showed

that tachycardia, dysrhythmias or cardiac murmurs can be found in horses with AM.<sup>34,35</sup> Our study confirmed the increased prevalence of VPDs indicating cardiac cellular injury.<sup>2,3</sup> In addition, and for the first time, QT prolongation could be linked to a specific disease in the horse. This finding can aid in the ante-mortem diagnosis of AM in horses and may also help unraveling the pathophysiology of the disease, which is currently not completely understood. Morphopathological data have revealed an accumulation of lipid droplets into affected skeletal muscles and a degeneration of predominantly type I muscle fibers.<sup>36</sup> Because type I, or slow contracting, fibers have a mainly aerobic-oxidative metabolic profile associated with the presence of numerous mitochondria, and the main function of muscle mitochondria is oxidative phosphorylation for energy production using fatty acids as the main substrate, the central role of mitochondria in the pathophysiology of AM became apparent.<sup>36,37</sup> Further research pointed towards an acquired multiple acyl-CoA dehydrogenase deficiency (MADD).<sup>37,38</sup> In mice, a link between very long-chain acyl-CoA dehydrogenase deficiency (VLADD) and long QT has been found.<sup>39</sup> VLADD has also been associated with alterations in intracellular calcium homeostasis,<sup>40</sup> potentially leading to dysrhythmias which we described in ten out of twelve horses with AM. Hence, our study supports the role of MADD in the pathophysiology of AM.

Until now, sudden death in horses with AM was attributed to cardiac failure.<sup>36,41</sup> The long QT interval we described in our study provides an alternative explanation for the high mortality rate associated with AM. Long QT in human medicine is related to an increased risk for the development of ventricular dysrhythmias such as ventricular fibrillation and Torsade de Pointes.<sup>42</sup> Furthermore, the potential protective role of docosahexaenoic acid (DHA), an omega-3 polyunsaturated fatty acid, against QT prolongation warrants further investigation.<sup>43,44</sup> In VLADD mice, a cardiac-specific reduction of DHA in the membrane phospholipids has been noticed.<sup>39</sup> If this reduction is also present in horses with AM, DHA supplementation could protect against the development of dysrhythmias, potentially reducing the high mortality associated with AM.

Despite numerous reports on AM in horses, ECG alterations were never reported. This finding supports the fact that the lack of standardization and diagnostic criteria in equine ECG hampers further development and application of the technique. Better standardization and analysis of multiple lead recordings will improve knowledge on

equine dysrhythmias and conduction disturbances. We advise that in all AM horses, an ECG should be recorded, preferably using the base-apex lead configuration, and recordings should be analyzed not only for rate and rhythm disturbances, but also for changes in duration of different waves and segments. Horses that survive should be followed-up by echocardiography and electrocardiography as our study showed that one horse still showed signs of cardiac disease. The presence of VPDs and QT<sub>c</sub> prolongation might still represent a risk factor for the development of ventricular tachydysrhythmias in these horses. Histopathological changes in the myocardium varying from mild to severe degeneration and necrosis of myocardial cells have been identified in AM horses and can be the cause of ectopy.<sup>36,45,46</sup> The horse in our study did not show signs of fibrosis on echocardiography. However, one should be aware that the ectopic focus and associated lesion might be very small and too small to be visualized on ultrasound. More studies are necessary to establish the extent of cardiac lesions and to evaluate restoration of cardiac function in surviving horses.

During the studies on atrial fibrillation and atypical myopathy, a number of problems were encountered which were due to a lack of knowledge regarding the equine ECG.

There is a lack of data describing the occurrence of dysrhythmias in normally performing horses, a prerequisite for evaluation of deviating findings. Most studies focused on horses with poor performance<sup>47,48</sup> or included only a small number of horses.<sup>49,50</sup> Furthermore, there is hardly any information on the variation of repeated electrocardiographic examinations in the same horse. As a consequence, the clinical significance of some dysrhythmias is not well established. The most recent guidelines suggest that premature depolarizations are clinically important if more than two isolated premature depolarizations are present during peak exercise or if multiple premature depolarizations (>5) or pairs or paroxysms of premature depolarizations are detected during peak exercise or immediately after exercise.<sup>47</sup> However, a much higher number of premature depolarizations was found in a study on cardiac dysrhythmias in normally performing Thoroughbreds,<sup>51</sup> suggesting that the current guidelines need to be re-evaluated. In two recent studies, the prevalence and frequency of cardiac dysrhythmias during exercise and recovery were documented for normally performing show jumping and dressage horses.<sup>2,3</sup> In show jumping horses, atrial premature depolarizations (APDs) were found in 32% of the horses at rest, 89% during exercise and 54% during recovery. VPDs were present in 18% of the horses during exercise and

7% during recovery. In dressage horses, APDs occurred rarely at rest, but in 29% of the horses during exercise and 62% of the horses during recovery. VPDs were present in 5% of the horses and occurred only during exercise. Although both studies were performed in warmblood horses, important differences existed in the prevalence and frequency of different dysrhythmias. In both studies ECG recordings were only performed once. Obviously, there is a need for studies repeatedly assessing the prevalence of dysrhythmias in a large number of healthy horses performing at different disciplines, using a standardised, multiple lead ECG protocol. These normal data will allow a better assessment of the importance of dysrhythmias in the healthy, poorly performing and diseased horse.

A second issue in the studies on AF and AM was the influence of electrolyte disturbances on equine ECG. Electrolyte disturbances may generate or facilitate cardiac dysrhythmias. They exert their action by modulating the conduction of ions across specific cardiac membrane channels. Involved ions are mainly potassium and calcium. Electrophysiological effects of sodium are rarely clinically significant. In human medicine, ECG changes induced by electrolyte disturbances and their associated dysrhythmias are well studied. Hypokalemia produces characteristic changes that are primarily due to delayed ventricular repolarization.<sup>52</sup> The result is ST-segment depression, decreased amplitude and broadening of T waves and U wave prominence.<sup>52,53</sup> In more severe hypokalemia, increased QRS duration, increased P wave amplitude and duration and prolonged PR interval may all occur.<sup>53</sup> Patients with hypokalemia are at risk for re-entrant dysrhythmias and Torsade de Pointes.<sup>52</sup> Hyperkalemia causes a distinctive sequence of ECG changes. The earliest changes are associated with an abnormally rapid repolarization and include the appearance of peaked, narrow-based T waves and a shortened QT interval. When plasma potassium concentration  $>7-8\text{mEq/L}$ , widening of the QRS complex and decreased amplitude with widening and eventual loss of the P wave occur, reflecting delayed depolarization. Sometimes, PR prolongation and ST depression develop in association with severe hyperkalemia. At higher concentrations a sine-wave pattern may develop, in which widened QRS complexes merge with the T wave, followed by ventricular fibrillation or asystole.<sup>52,53</sup> The ECG changes of hypocalcaemia are due to prolongation of the action potential duration and involve a prolongation of the ST segment and QT interval and T wave alterations. This renders patients more susceptible to ventricular dysrhythmias.

Hypercalcaemia causes a shortening of the action potential duration and hence a shortened ST segment and decreased QT interval. Severe hypercalcaemia has been reported to result in bradydysrhythmias and atrial fibrillation.<sup>54</sup> Hypomagnesaemia and hypermagnesaemia do not produce specific ECG segment changes.<sup>52,53</sup> Electrophysiological effects of sodium are rarely clinically significant.<sup>53</sup> There is some debate as to whether hypomagnesaemia causes dysrhythmias in healthy subjects,<sup>55,56</sup> but in patients with cardiac disease, mild hypomagnesaemia is associated with ventricular dysrhythmias.<sup>55</sup>

In horses, the association between electrolyte disturbances and electrocardiographic changes and dysrhythmias is less clear. Most textbooks and review articles refer to research from human and small animal medicine, and only a few original articles are published. Experimentally induced hyperkalemia is reported to result in a progressive broadening and flattening of the P wave, with disappearance of the P wave at plasma potassium levels of 8.5 to 9.1 mmol/L. T waves became inverted and peaked. At plasma potassium levels of 8.0 to 10.1 mmol/L, dysrhythmias such as atrial premature beats, AV dissociation, ventricular premature beats, ventricular tachycardia and cardiac arrest became evident.<sup>57,58</sup> Experimentally induced electrolyte disturbances can never truly mimic clinical circumstances in which many factors interact. Therefore, differences between experimental findings and clinical observations can arise. In colic horses, hypocalcaemia and hypomagnesaemia resulted in a prolongation of the QT interval.<sup>59</sup> Although low concentrations of calcium and magnesium were measured, a low frequency of dysrhythmias was observed. This might indicate that horses have a higher threshold for the development of dysrhythmias in the face of low serum concentrations of calcium and magnesium. Clinical studies on the effect of different degrees of electrolyte disturbances on electrocardiographic recordings and dysrhythmias are needed to help assess their importance in horses with AM or AF.

A problem with analyzing duration of different ECG waves and segments, is the lack of information regarding normal findings in healthy horses at rest, but particularly during exercise and with increased heart rate often associated with disease. In human medicine, the QT interval is known to be influenced by age, gender and body mass index,<sup>60,61</sup> while gender and exercise influence QRS duration.<sup>62,63</sup> In the study on horses with AF, we described for the first time a significant shortening of the QRS complex during exercise. Literature describes that the normal equine QRS duration should be less

than 0.14 seconds.<sup>64</sup> However, the fact that increased heart rate results in QRS shortening means that these criteria should be adapted. It also means that the duration of abnormal QRS complexes (VPDs) during exercise may be less than 0.14 seconds and may lead to a wrong diagnosis when using current guidelines. In the study on horses with AM, we corrected the QT segments for heart rate using Fridericia's correction method. However, it is not known whether this correction method that has its origin in human medicine, is the most suitable correction method for horses. In addition, a correction for body weight might be required.<sup>65</sup> More detailed studies regarding electrocardiographic time intervals and the influence of heart rate, body weight, size, gender and age are needed in horses.

In order to do so, a better standardization of equine electrocardiography is necessary. In human medicine, the importance of a standardized positioning of electrodes to improve the accuracy and usefulness of the ECG is well recognized.<sup>66</sup> Improper placement of recording electrodes can generate misleading patterns on the ECG, which can mimic cardiac or noncardiac conditions.<sup>67-69</sup> The use of multiple lead recordings has led to an enormous advancement in the diagnosis and understanding of cardiac diseases. Despite the fact that vector analysis cannot be applied in horses, standardization of electrode positioning and the use of multiple leads are mandatory to further develop equine electrocardiography.

In chapters 5 and 6 of this thesis, new ECG recording techniques with specific advantages compared to surface ECG recording were studied.

A limitation inherent to surface ECG is the small amplitude of atrial depolarizations when compared to the massive deflections associated with the depolarization of the ventricles. In both human and small animal medicine, esophageal ECG has been developed decades ago to magnify the atrial deflections and hence aid in the diagnosis of supraventricular tachydysrhythmias. Our study is the first to describe esophageal recordings in horses. The most important advantage of esophageal ECG is the magnification of P waves relative to the QRS complex which allows a more accurate diagnosis of tachydysrhythmias.

Esophageal recordings during walk were of disappointing quality. Excessive baseline wandering made all recordings unsuitable for diagnostic purposes. In the early days of esophageal ECG recording in man, similar baseline wandering, although at rest, hampered the use of the technique in clinical practice. Use of a preamplifier which

filtered out frequencies between 5 Hz and 100 Hz eliminated baseline wander.<sup>70</sup> Refiltering the recorded esophageal ECG signals in horses using this bandwidth, might also improve the quality of the recorded esophageal ECGs. If quality of recordings during exercise cannot be improved, the practical use of esophageal ECG recordings in horses will be limited to resting recordings. Esophageal ECG recording did allow significant magnification of P waves relative to QRS complexes and T waves. Electrode positions were optimized for recording of atrial activity. Intra-esophageal as well as combined surface-esophageal electrode positions were described and will allow further studies on the origin of tachydysrhythmias.

The optimal electrode position for recording atrial activity implies that this electrode position might also be used for temporary cardiac pacing. Cardiac pacing in horses has been applied to treat bradycardia and atrial flutter.<sup>71</sup> Besides, cardiac pacing has been used to perform electrophysiological studies in horses.<sup>26</sup> Although in dogs currently only atrial transesophageal pacing has been achieved, preliminary results from our department show that in horses also ventricular pacing through the esophagus is achievable.

In human medicine, esophageal recordings are made using an interelectrode distance of 1-3 cm.<sup>72,73</sup> This short interelectrode distance results in esophageal ECG recordings with very clear and sharp atrial deflections, approximating intra-atrial recordings. Furthermore, the small interelectrode distance allows for selective atrial pacing via the esophagus. Because the esophageal ECG in human patients allows precise timing of the different cardiac events it has become a valuable diagnostic tool for classification of tachydysrhythmias.<sup>70,72,74</sup> In our study in horses, we used a commercially available quadripolar esophageal catheter with an interelectrode distance of 10 cm. Due to this relatively large distance the electrogram does not represent focal electrical activity but is rather comparable to a bipolar surface ECG recording. In our study, an interelectrode distance of 10 cm gave the best results for recording atrial activity from within the esophagus (largest P wave). Since this was the shortest interelectrode distance available on the catheter, we were not able to test whether shorter distances would lead to even larger P wave amplitudes or to a more focal registration of atrial activation. Due to the larger distance between esophagus and atrium in horses compared with humans, it seemed unlikely that more closely spaced electrodes were of benefit. The large interelectrode distance did not hamper the goal of our study which was to magnify P

wave amplitude with respect to QRS complex. The larger interelectrode spacing and the distance between esophagus and heart probably require higher currents and pulse durations in order to achieve atrial or ventricular pacing. Reducing interelectrode distance could theoretically reduce the pacing threshold<sup>75</sup> and allow for a more focal atrial activation.

The study on intra-atrial electrocardiography shows that recording the electrical activity from within the heart is feasible in standing, unsedated horses. The latter is important since sedatives can influence cardiac electrophysiology and hence hamper the diagnosis of certain dysrhythmias. Using a pacing catheter, placed in the right atrium and connected to a digital recording unit, atrial depolarization could accurately be detected and atrial fibrillation cycle length (AFCL) easily be determined.

For the first time, potential factors predicting risk for AF recurrence after electrical cardioversion were identified in horses. Such information is very important in a clinical setting in order to make correct diagnostic, therapeutic and prognostic decisions. Local AFCL was measured because it correlates with atrial effective refractory period (AERP),<sup>76</sup> which is a measure for electrical remodeling of the atria. A short AERP is associated with a higher risk for the development of dysrhythmia as it promotes the coexistence of multiple re-entrant wavelets and hence provides a superior substrate for AF maintenance.<sup>77</sup> Expectation was that a shorter AFCL would be related to an increased AF susceptibility and therefore risk for AF recurrence. Although our study indicated that mean AFCL was indeed a significant risk factor for the prediction of AF recurrence, the significance level was low. This might be explained by the fact that after restoration of sinus rhythm, reverse electrical remodeling occurs rapidly,<sup>26,27,78</sup> reducing vulnerability to AF recurrence. Therefore, AFCL might have a more important role in predicting short-term AF recurrence. Another explanation might be that the AFCL does not always predict the same degree of remodeling: horses with a similar AFCL might have a different baseline AERP and therefore a different susceptibility and recurrence rate. In addition, differences in AF duration influenced the AFCL. Studies suggest that electrical remodeling develops quickly, following a logarithmic curve of rapid initial decline and gradual late decay.<sup>27,79</sup> It is likely that horses were electrically remodeled to different degrees according to the AF duration.

AF duration was not significantly different between horses maintaining sinus rhythm and those suffering from AF recurrence. This finding is in contrast to studies in human

medicine, where AF duration is one of the factors showing consistent value for the prediction of recurrence.<sup>80</sup> Also in horses it has been suggested that animals with chronic AF were more likely to show AF recurrence.<sup>81,82</sup> Including a larger number of horses in our study could have resulted in a significant difference between the two groups of horses. On the other hand, it is also possible that a long AF duration prior to treatment has no significant influence on recurrence rate in horses. Horses (at rest) tolerate AF very well and do not show the resting tachycardia or progressively worsening of symptoms associated with AF in human medicine.<sup>83</sup> In addition, electrical remodeling in horses has been shown to occur mainly in the first few weeks after AF induction, and is attenuated in later stages.<sup>26,27,78</sup> As such, it is possible that AF recurrence is not strongly related to AF duration in horses.

Increased left atrial size was found to be another potential risk factor for AF recurrence. This seems not surprising, since the inducibility of AF depends on the ability of the atria to maintain a critical number of re-entrant waves and a larger atrial mass allows the coexistence of multiple wavelets. However, in human medicine, data concerning the predictive value of left atrial size for AF recurrence are conflicting.<sup>84</sup>

In agreement to findings in human medicine, the ratio of 5<sup>th</sup> percentile of AFCL to left atrial diameter was found to be a risk factor for AF recurrence<sup>85</sup>, as was the ratio of 5<sup>th</sup> percentile AFCL to left atrial size relative to aortic diameter. These results are interesting as they combine different aspects of atrial fibrillation, i.e. electrical remodeling and atrial size. However, predictive power of both parameters was rather low, suggesting that other factors may play a role. One such parameter could be ectopic foci that induce AF. A high burden of ectopic impulses is likely to re-induce AF, even if electrophysiological characteristics or atrial size are not optimal for AF. In human medicine as well as in studies in dogs and goats, structural remodeling has been described in association with AF. Induced changes included ultrastructural degeneration of atrial myocytes,<sup>86,87</sup> accumulation of glycogen,<sup>88</sup> cardiomyocyte dedifferentiation<sup>89</sup> and gap junction remodeling.<sup>90</sup> Recovery from AF induced structural remodeling after restoration of sinus rhythm has been shown to be a very slow process,<sup>87</sup> with several changes still present to a significant degree after four months follow-up.<sup>91</sup> It can be expected that AF recurrence is more likely as long as structural changes are present. Currently, no information is available regarding the induction of structural changes due to AF in horses, but it has been shown that horses with AF more frequently present

patchy atrial fibrosis. Currently, such fibrosis cannot be detected by cardiac ultrasound in horses and therefore the importance remains unknown in horses with AF.

None of the investigated parameters proved to have a very strong predictive power for the maintenance of sinus rhythm after cardioversion. However, despite the low number of horses in our study, findings were very similar to findings in human medicine. Including a larger number of horses in the study and standardizing the follow-up period might result in stronger predictive powers or the identification of other parameters that are important in the risk stratification for AF recurrence.

The simplicity of the technique described in our study is promising for the future use of intracardiac ECG recordings in electrophysiological studies. As in human medicine, the technique could be used for the recognition and understanding of several cardiac dysrhythmias. Intracardiac recording might allow recording of the entire atrioventricular conduction system, and, when combined with surface ECG recording, the differentiation between supraventricular or ventricular tachycardias.

A difficulty that might arise is the large size of adult horses, requiring special, long catheters but also adapted techniques for catheter placement. Echocardiography, rather than radiography, has proven to be the most suitable method for guiding catheter placement.<sup>92</sup> The large atrial and ventricular size might enhance catheter movement and dislodgement. Finally, although the cardiac conduction system is suggested to be common in most animal species,<sup>93</sup> it has been poorly described in horses and precise anatomical landmarks to retrieve the different parts of the conduction system are not available.

Currently, the treatment of choice for horses with lone AF is transvenous electrical cardioversion. The technique has a high success rate, but in a small percentage of horses restoration of sinus rhythm cannot be achieved. More importantly, recurrence of AF occurs in 15 to 35 % of the horses. In human medicine, catheter ablation is an established treatment for AF, with clinical trials demonstrating superior outcomes for catheter ablation compared to antiarrhythmic drug therapy.<sup>94</sup> Especially long-term success is better since the technique attempts to prevent recurrence by isolating the pulmonary veins, which are known to be the origin of the rapidly firing foci that initiate AF.<sup>95</sup> Currently, no information is available about the triggering factors for atrial fibrillation in horses. If intracardiac electrography can be developed further to a level where electrophysiological studies and cardiac mapping allow localization of the trigger

of AF, alternative therapies such as ablation might be investigated to further increase the long-term success rate of AF treatment in horses.

#### Conclusions and future prospects

This work reveals new diagnostic and potentially therapeutic applications in the field of equine electrocardiography. The studies on horses with atrial fibrillation and atypical myopathy demonstrate that standardization of the technique and better analyses of the results allow for a better detection of cardiac disorders and contribute to new insights into the pathophysiology of conditions affecting the heart.

Besides the diagnostic value of esophageal electrocardiography, the esophagus could provide an easy and minimally invasive route for atrial and ventricular pacing. The technique is likely to be effective in preventing bradycardia or asystole during anesthesia of 'at risk' patients, such as those with symptomatic bradycardia or hyperkalemia due to bladder rupture.

Further development of intracardiac electrography will greatly enhance our understanding of intracardiac conduction disorders and cardiac dysrhythmias in horses. It will enhance differentiation between supraventricular and ventricular tachydysrhythmias and hence, help to fine-tune diagnostic criteria on the surface ECG. At the same time, intracardiac electrodes might be used to identify the origin of ectopic foci and explore the applicability of ablation techniques.

In order to upgrade equine electrocardiography, a uniform electrode position and multiple lead recording needs to be introduced. Future research should first be devoted to the further standardisation of ECG recording techniques and identify normal ECG findings for different breeds, animal size and weight, gender, age, heart rate,... These results will allow to better identify abnormal findings in different disease states.

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# SUMMARY



Since the development of the string galvanometer by Einthoven, electrocardiography in human medicine has become the most commonly conducted cardiovascular diagnostic procedure and a fundamental tool of clinical practice. It is not only used for the diagnosis of dysrhythmias, but also allows recognition of electrolyte abnormalities, conduction disturbances, genetically mediated electrical or structural cardiac abnormalities and myocardial infarction. Similarities between human and small animal cardiac conduction system have led to an extensive knowledge of small animal electrocardiography.

Equine electrocardiography has not followed this evolution, largely due to the difference in conduction system in horses, with concomitant reduction of the amount of information that can be obtained from a surface ECG recording. Our research shows that despite this limitation, equine electrocardiography can be developed further and has the potential to be of interest for more than rate and rhythm analysis.

The General Introduction discusses general features of electrocardiography. First, the electrical properties of the heart leading to the generation of an electrocardiogram are briefly discussed. Subsequently, an overview is presented of the development of electrocardiography in human and small animal medicine, which is in contrast to that in equine medicine.

Chapter 1 summarizes the current use of equine electrocardiography. The first part describes the standard ECG recording technique in horses, while in the second part the most commonly occurring dysrhythmias and their appearance on the surface ECG are discussed.

In Chapter 2, the aims of this thesis are described. The first objective of this dissertation was to evaluate the potential clinical significance of surface ECG recordings in two diseases that affect the heart (Chapters 3 and 4). The second objective was to explore and evaluate new electrocardiographic recording techniques that allow for a better recording of atrial electrical activity compared to surface ECG recordings (Chapters 5 and 6).

Chapter 3 describes specific dysrhythmias associated with atrial fibrillation (AF) in horses. AF is the most important dysrhythmia affecting performance in horses and has been associated with incoordination, collapse and sudden death. Limited information is available on ventricular response during exercise in horses with lone AF. A modified base-apex ECG was recorded from 43 horses diagnosed with lone AF at rest, during a

standardized lunging exercise and during a short recovery period. During the standardized lunging exercise horses were walked seven minutes, trotted ten minutes, cantered four minutes and galloped one minute. Designated recovery period was seven minutes.

In all horses, a disproportionate tachycardia was present during exercise and individual beat-to-beat maximal heart rate was above the upper heart rate limit for maximally performing horses. In addition, the prevalences of QRS broadening and the R-on-T phenomenon were extremely high, occurring in 81% and 33% of the cases, respectively. Whether these broad QRS complexes are supraventricular or ventricular in origin, is currently unclear. The high prevalence of these dysrhythmias in horses with AF could be a risk factor for the development of ventricular tachycardia, even at low levels of exercise, and could explain the signs of weakness, collapse and sudden death in horses with AF.

In [Chapter 4](#), for the first time, prolongation of the (corrected) QT interval ( $QT_c$ ) is linked to a specific disease in horses. Atypical myopathy (AM) is an acute, highly fatal rhabdomyolysis in grazing horses that mainly affects skeletal muscles. Post mortem examinations have shown that myocardial damage also occurs. Limited information is available on the effect of AM on cardiac function in affected and surviving horses.

Twelve horses diagnosed with AM underwent clinical examination, serum biochemistry, electrocardiography and echocardiography. Four surviving horses underwent the same examinations after 2 to 10 weeks.

Results confirmed the presence of cardiac damage in horses with AM, as demonstrated by the elevated concentration of cardiac troponin I and the presence of ventricular premature depolarisations (VPDs). In addition, all horses showed a prolonged  $QT_c$  interval, demonstrating that AM can result in consistent alterations on electrocardiography. One horse still showed VPDs and a prolonged  $QT_c$  at ten weeks follow-up, suggesting that full recovery had not occurred.

These two chapters demonstrate that a standardized approach to electrocardiography in horses increases the diagnostic value of the technique. Furthermore, electrocardiography can contribute to unravel the pathophysiology of cardiac diseases.

In [Chapter 5](#), the feasibility and usefulness of esophageal electrocardiography in horses are described. In human medicine, esophageal electrocardiography is a well-established technique that magnifies P waves with respect to the QRS complex.

Bipolar and unipolar ECG recordings were made using intra-esophageal and body surface electrodes. An esophageal catheter with electrodes was inserted into the esophagus. At maximal depth, three intra-esophageal and three combined esophageal-surface recordings were made consecutively. At the same time, a base-apex ECG was recorded continuously. While gradually withdrawing the esophageal catheter, recordings from all six electrode configurations were made every ten cm. At optimal electrode positions, i.e. when large P wave amplitudes were present, horses were walked at hand for recording of all combinations during physical movement. In addition, at each recording depth, three consecutive unipolar recordings were made. Amplitudes of P, Q, R, S and T waves were measured from three different cardiac cycles for each recording configuration and depth.

Results showed that esophageal ECG recording is a safe, simple and effective technique to record cardiac electrical activity and to amplify the atrial electrical signal in healthy horses at rest. Recordings during movement resulted in important baseline wander and did not allow accurate interpretation. The procedure is a promising tool to diagnose and study supraventricular and ventricular tachydysrhythmias at rest. Additionally, the optimal electrode configurations might be used in the future to perform electrophysiological studies and to treat bradycardia by temporary pacing.

[Chapter 6](#) describes the use of intra-atrial electrogram recording in horses and investigates the predictive value of atrial fibrillation cycle length (AFCL) and atrial size for AF recurrence. In human medicine, intra-atrial electrograms are used to determine AFCL, a parameter used to assess the risk for AF recurrence. In horses, no simple technique to determine AFCL is available, and criteria to predict AF recurrence have not been studied.

Estimated AF duration, echocardiographic parameters and AFCL were determined prior to transvenous electrical cardioversion (TVEC) in 21 horses. The follow up time after restoration of sinus rhythm ranged from 3.5 months to 3 years.

Results showed that intra-atrial electrograms of high quality can be recorded in horses using a simple technique, allowing accurate local AFCL determination. Left atrial diameter, mean AFCL, ratio of 5<sup>th</sup> percentile AFCL to left atrial diameter and ratio of 5<sup>th</sup>

percentile AFCL to left atrial diameter related to aortic diameter were all significantly different between horses that maintained sinus rhythm and those suffering from AF recurrence.

Our study shows that intracardiac electrogram recording can be performed relatively easily and is a promising pre-treatment tool in horses with AF to assess risk for AF recurrence. In addition, the technique can be used to perform electrophysiological studies in horses.

These two chapters demonstrate that new ECG recording techniques have specific advantages compared to surface ECG. Further development of esophageal and intracardiac recording techniques will lead to an increased understanding and diagnostic accuracy of dysrhythmias. Furthermore, knowledge from both studies can be used to further develop intracardiac electrophysiological studies, cardiac pacing or even ablation techniques.

As a General conclusion this work shows that equine electrocardiography has important diagnostic and therapeutic value that is currently underinvestigated. With the results from our studies as a starting point, further research into electrocardiographic abnormalities and new recording techniques will allow for equine electrocardiography to evolve to a higher level. However, future research should first be devoted to the standardisation of ECG recording techniques and the importance of electrode position and multiple lead recordings. Identification of the influence of exercise and differences in breed, animal size and weight, gender, age and heart rate on normal ECG findings is necessary to allow a better recognition of abnormal findings in diseased horses.

# SAMENVATTING



Sinds Einthoven de snaargalvanometer ontwikkelde, evolueerde electrocardiografie in de humane geneeskunde tot de onmisbare en meest gebruikte techniek voor de diagnose van cardiovasculaire aandoeningen die het vandaag is. Electrocardiografie wordt niet alleen gebruikt voor de diagnose van dysritmieën, maar ook voor het opsporen van stoornissen in elektrolyten balans, geleidingsstoornissen, elektrische of structurele hartafwijkingen met een genetische grondslag of myocard infarcten. De sterke gelijkenissen tussen het hartgeleidingssysteem van mens en kleine huisdieren, hebben ertoe geleid dat ook in de geneeskunde van de kleine huisdieren een uitgebreide kennis over electrocardiografie bestaat.

Bij paarden is de evolutie en daardoor ook de kennis van electrocardiografie beperkt gebleven. De oorzaak hiervoor moet gezocht worden in het hartgeleidingssysteem dat anders verloopt bij paarden, wat de informatie die kan afgeleid worden uit een oppervlakte ECG reduceert. Ons onderzoek toont echter aan dat, ondanks deze beperking, de techniek van electrocardiografie bij paarden verder ontwikkeld kan worden zodat het gebruik ervan niet beperkt blijft tot de analyse van hartfrequentie en hartritme.

De algemene principes van electrocardiografie worden uiteengezet in de introdunctie van deze thesis. Eerst worden de elektrische eigenschappen van het hart die leiden tot de generatie van een electrocardiogram kort vermeld. Vervolgens wordt een overzicht geschetst van de evolutie van de electrocardiografische techniek bij mensen en kleine huisdieren, in contrast tot die bij paarden.

Hoofdstuk 1 vat het huidige gebruik van electrocardiografie bij paarden samen. Het eerste deel beschrijft courant gebruikte ECG opname systemen. In het tweede deel wordt dieper ingegaan op de electrocardiografische diagnose van de meest voorkomende dysritmieën bij paarden.

Het onderzoeksdeel van deze thesis bestaat uit twee grote delen. Het **eerste deel** (Hoofdstukken 3 en 4) beschrijft het klinische belang van electrocardiografie bij paarden bij twee ziekten met een invloed op het hart. Voor beide ziektebeelden worden specifieke en klinisch relevante electrocardiografische bevindingen beschreven die tot nu toe onbekend waren. Het **tweede deel** (Hoofdstukken 5 en 6) beschrijft de ontwikkeling van nieuwe electrocardiografische technieken die specifieke voordelen bieden ten opzichte van het oppervlakte ECG.

Hoofdstuk 3 beschrijft specifieke dysritmieën bij paarden met atriale fibrillatie (AF). AF is de belangrijkste prestatie beïnvloedende dysritmie bij paarden en wordt soms geassocieerd met incoördinatie, collaps en zelfs plotse dood. Weinig is bekend over de ventriculaire respons van paarden met primaire AF tijdens werk. Bij 43 paarden met een bevestigde diagnose van primaire AF werd een gemodificeerd base-apex ECG opgenomen tijdens rust, een gestandaardiseerde longertest en recuperatie. De longertest bestond achtereenvolgens uit zeven minuten stap, tien minuten draf, vier minuten arbeidsgalop en een minuut volle galop.

Alle paarden vertoonden een disproportionele tachycardie tijdens werk en een individuele maximale hartslag die hoger was dan de normale bovengrens voor maximaal presterende paarden. Extreem hoge prevalenties werden gevonden voor QRS verbreding (81% van de paarden) en het R-op-T fenomeen (33% van de paarden). Of de oorsprong van deze QRS verbreding supraventriculair of ventriculair gezocht moet worden, is momenteel onduidelijk. De hoge prevalentie van deze dysritmieën bij paarden met AF is een mogelijke risicofactor voor het ontwikkelen van ventriculaire tachycardie, zelfs bij lage werkkintensiteit, en kan een verklaring zijn voor het voorkomen van incoördinatie, collaps en plotse sterfte bij paarden met AF.

In hoofdstuk 4 wordt, voor de eerste keer, prolongatie van het (gecorrigeerde) QT interval ( $QT_c$ ) gelinkt aan een specifieke ziekte bij paarden. Atypische myopathie (AM) is een acute rhabdomyolyse die vaak fataal verloopt en hoofdzakelijk skeletspieren aantast. Post mortem onderzoek heeft aangetoond dat ook myocardschade kan optreden. De beschikbare informatie over het effect van AM op de hartfunctie in zieke en overlevende paarden is echter erg beperkt.

Bij twaalf paarden gediagnosticeerd met AM werden een klinisch, biochemisch, electrocardiografisch en echocardiografisch onderzoek uitgevoerd. Bij vier overlevende paarden werden dezelfde onderzoeken herhaald na twee tot tien weken.

De verhoogde concentraties aan cardiaal troponine I en de aanwezigheid van ventriculaire premature depolarisaties (VPDs) bevestigden de aanwezigheid van myocardschade bij paarden met AM. Bovendien vertoonden alle paarden een verlengd  $QT_c$  interval, wat aantoont dat AM resulteert in consistente veranderingen op het ECG. Bij een van de overlevende paarden werden nog steeds VPDs en een verlengd  $QT_c$  aangetroffen na een follow-up periode van tien weken, wat aantoont dat het herstel nog niet volledig was.

Deze twee hoofdstukken tonen aan dat een gestandaardiseerde aanpak van elektrocardiografie nodig is om tot een accurate diagnose te komen. Bovendien kan de techniek bijdragen tot het ontrafelen van de pathofysiologie van ziekten die een invloed hebben op het hart.

In hoofdstuk 5 worden de techniek en de meerwaarde van een oesofagaal ECG bij paarden beschreven. In de humane geneeskunde is het oesofagaal ECG een erkende techniek voor het vergroten van de P golf ten opzichte van het QRS complex.

Met behulp van intra-oesofagale en oppervlakte elektrodes werden bipolaire en unipolaire ECGs opgenomen. Een oesofagale katheter met elektrodes werd opgeschoven in de slokdarm tot de maximale diepte bereikt werd. Daar werden achtereenvolgens drie intra-oesofagale en drie gecombineerde oesofagaal-oppervlakte ECG opnames gemaakt. Tegelijkertijd werd een base-apex ECG opgenomen. Tijdens het gradueel terugtrekken van de katheter, werden elke tien centimeter opnames gemaakt van alle zes elektrode configuraties. Bij een optimale positie van de elektrodes, daar waar grote P golf amplitudes opgemerkt werden, werden de paarden aan de hand gestapt om opnames te maken tijdens beweging. Bovendien werden op elke opname diepte achtereenvolgens drie unipolaire opnames gemaakt. De amplitudes van P, Q, R, S en T golven werden gemeten aan de hand van drie hartcycli voor elke opname configuratie en diepte.

Uit de resultaten blijkt dat oesofagaal ECG een veilige, eenvoudige en effectieve techniek is om de hartactiviteit van paarden te registreren en om het atriale elektrische signaal te vergroten. De artefacten die ontstonden tijdens beweging verhinderden een accurate interpretatie van de dan geregistreerde ECGs. Oesofagaal ECG is een veelbelovende techniek voor de diagnose en studie van supraventriculaire en ventriculaire tachydysrhythmieën in rust. Bovendien kan de beschreven optimale elektrode configuratie in de toekomst gebuikt worden voor het uitvoeren van elektrofysiologische studies en de behandeling van bradycardie door temporair pacen.

Hoofdstuk 6 beschrijft het gebruik van intra-atriale ECGs bij paarden en de voorspellende waarde van atriale fibrillatie cyclus lengte (AFCL) en atriale diameter voor AF herhal. In de humane geneeskunde wordt gebruik gemaakt van een intra-atriaal electrogram om AFCL te bepalen, een parameter die gebruikt wordt voor het inschatten van de kans op herhal van AF. Bij paarden is er momenteel geen eenvoudige techniek om

AFCL te bepalen en zijn er geen criteria beschikbaar om de kans op herval van AF in te schatten.

Bij 21 paarden met AF werd de AF duur geschat, een volledig echocardiografisch onderzoek uitgevoerd en een intra-atriaal electrogram afgenomen om de AFCL te bepalen. Na behandeling met transveneuze elektrische cardioversie werden de paarden tussen 3.5 maanden en 3 jaar opgevolgd om herval van AF op te sporen.

Uit de resultaten blijkt dat de beschreven methode voor het opnemen van intra-atriale electrogrammen een eenvoudige techniek is die toelaat op nauwkeurige wijze de AFCL te bepalen. De linker atriale diameter van links gemeten (LLA), de verhouding van het vijfde percentiel van de AFCL (p5AFCL) tot de LLA, de verhouding van p5AFCL tot de LLA in relatie tot de diameter van de aorta en de gemiddelde AFCL waren significant verschillend tussen paarden die in sinus ritme bleven en paarden die hervielen in AF.

De beschreven techniek bleek dus vlot toepasbaar en veelbelovend om het risico op AF recidief in te schatten, bv alvorens een therapie wordt ingesteld. Daarenboven kan deze techniek in de toekomst ook gebruikt worden om elektrofysiologische studies bij paarden uit te voeren om de kennis van de electrofysiologie van het paardenhart te vergroten.

Deze twee hoofdstukken tonen aan dat nieuwe technieken voor het registreren van een ECG specifieke voordelen hebben ten opzichte van het oppervlakte ECG. Door het verder ontwikkelen van oesofagale en intracardiale opname technieken zal de kennis van dysritmieën en hun accurate diagnose verbeterd kunnen worden. Bovendien kunnen gegevens uit beide studies gebruikt worden voor de ontwikkeling van intracardiale elektrofysiologische studies, pacen van het hart of misschien zelfs ablatie technieken.

In Conclusie toont dit werk aan dat electrocardiografie bij paarden een belangrijke diagnostische en therapeutische meerwaarde kan betekenen die momenteel te weinig onderzocht is. Met de resultaten van onze onderzoeken als startpunt kan, door verdere studies naar electrocardiografische afwijkingen en nieuwe registratie technieken, electrocardiografie bij paarden naar een hoger niveau getild worden. Van het grootste belang daarbij is echter dat eerst onderzoek gevoerd wordt naar de standaardisatie van ECG registratie technieken, het belang van elektrode positie en de registratie van meerdere afleidingen. Identificatie van normale ECG bevindingen voor verschillen in

paardenras, schofhoogte, gewicht, geslacht, leeftijd en hartfrequentie is nodig om abnormale bevindingen bij ziekten beter te kunnen onderscheiden.



# CURRICULUM VITAE



Tinne Verheyen werd geboren op 18 december 1980 in Lier. Na het beëindigen van het secundair onderwijs aan het Kardinaal Van Roey Instituut in Vorselaar, richting Latijn-Wetenschappen, begon zij in 1998 aan de studie Diergeneeskunde aan de Universiteit van Gent en behaalde in 2004 met onderscheiding het diploma van dierenarts.

In 2005 trad zij als voltijds assistent in Dienst bij de vakgroep Farmacologie, Toxicologie, Biochemie en Orgaanfysiologie, waar zij instond voor het geven van practica fysiologie aan de studenten van het tweede jaar diergeneeskunde. In 2008 werd ze geïntegreerd in de vakgroep Inwendige Ziekten en Klinische Biologie van de Grote Huisdieren, waar zij ingeschakeld werd in het cardiologisch onderzoek onder leiding van Prof. Dr. Gunther van Loon. Naast het geven van practica startte zij wetenschappelijk onderzoek naar het gebruik van elektrocardiografie bij paarden, wat leidde tot deze doctoraatsthesis. Daarnaast volgde zij ook de doctoraatsopleiding. In 2010 behaalde zij het diploma 'Toegepast Diergedrag' aan de Katholieke Hogeschool in Sint-Niklaas. Tevens behaalde zij in 2012 het diploma van de Doctoral School of Life Sciences and Medicine van de Universiteit Gent.

Tinne Verheyen is auteur of medeauteur van meerdere wetenschappelijke publicaties en gaf presentaties op verschillende nationale en internationale congressen. In 2012 won zij de "BEVA award" voor beste orale presentatie.



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Na een paar jaar belandde ik – ook weer bij toeval? – op de dienst Inwendige Ziekten van de Grote Huisdieren. Zoals bij iedereen die onder de vleugels van prof. dr. Gunther van Loon terecht komt, werd ook bij mij cardiologie mijn ding, en dan vooral de elektrocardiografie. Voor mij bestaat er niets mooiers: betaald worden om toe te kijken hoe andere mensen paarden longeren, om daarna de opgenomen ECGs te analyseren. Op de vaak gestelde vraag – meestal op een toon die medelijden verraadde – of ik dat niet enorm saai vond, al die ECGs, kon ik alleen maar oprecht en lichtjes verbaasd 'nee' antwoorden. De rust en eenzaamheid bij het analyseren, na een tijdje de routine die

ruimte liet voor een streepje muziek of het rondzwerven van de gedachten, en dan plots toch weer een verrassing die kon schuilen achter elke hoek, en tevoorschijn kwam met één klik van de muis...zalig! Ik ga het missen...

Naast ECGs opnemen, moest er natuurlijk ook nog onderzoek verricht worden, en welk onderwerp kon mooier zijn dan precies dat: electrocardiografie? Gunther, ik kan je onmogelijk genoeg bedanken voor alle raad, tijd, suggesties, verbeteringen, verbeteringen en verbeteringen die ik van je gekregen heb. Zonder jou was er geen doctoraat. Dankjewel! Maar ook voor alle niet-doctoraatsgerelateerde gesprekken: dankjewel, voor het luisteren en het begrip zonder oordeel, twee zeldzame kwaliteiten.

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Een paar mensen uit de vakgroep wil ik hier zeker vernoemen. Prof. dr. Piet Deprez, uw kennis en kunde zijn onovertroffen. Maar wat ik vooral nooit zal vergeten, is dat u me nooit het gevoel gaf er niet echt bij te horen. Bart en Sara, ergens zaten we in hetzelfde schuitje, bedankt voor de schouderklopjes en oprechte interesse, ze hebben ongelooflijk deugd gedaan! Hans, zonder jou geen vakgroep Inwendige Ziekten, bedankt voor het weer op gang krijgen van mijn gehackte computer, maar bovenal voor de welgemeende goeiemorgens elke dag, een klein gebaar met een grootse impact. Sylvie en Sabrina, jullie werk voor de vakgroep kan niet genoeg gewaardeerd worden en wordt dat waarschijnlijk ook niet, maar voor mij was vooral jullie morele steun onbetaalbaar. Wat zou ik toch geweest zijn zonder jullie... Bedankt! Kirsten, jij bent onmisbaar gebleken voor mijn mentale gezondheid. Onze middagwandelingen gaven de nodige zuurstof aan mijn bijtijds benevelde en mistige brein, en onze gesprekken waren als zalf op mijn gevoelige zieltje. Je Mega Mindy superpowers waren dan weer broodnodig bij de slokdarm-proef... Ook jij: bedankt! En dan kom ik bij mijn medeleden van het cardio-team. Dominique, mijn bureaugenoot maar ook zoveel meer, we zijn samen lastige periodes door gesparteld, en dan heb ik het niet over al die sondes bij al die lieve

proefpaarden. Ik heb heel wat geleerd van jou ten tijde van het examen om toegelaten te worden tot dat clubke, maar nog meer over de dingen die er echt toe doen in het leven. Ik ga onze gesprekken missen. Maar je weet me wonen: daar waar je rechtdoor moet voor de Gamma, maar eigenlijk naar links, is het naar rechts. Mijn deur staat altijd open. Annelies, jou eerste hulp bij statistische problemen is onovertroffen. Voor mij onoverkomelijk, voor jou kinderspel, dankjewel voor alle analyses in SPSS, en heranalyses, en heranalyses... Maar ook zonder die statistiek: je bent een fantastische madam, en ik ben blij dat je er was! En Nicky, mijn partner-in-crime, mijn lotgenoot op de Gauss-curve, jou ken ik het minst lang, maar ik heb het gevoel dat ik je het langste ken... Waar Gunther de leider is van ons cardio-dreamteam, Dominique de ervaringsdeskundige en Annelies de hersenen, ben jij het hart: altijd inspringen, altijd helpen, altijd enthousiast. Als ik een Amerikaanse was, zou ik waarschijnlijk regelmatig 'lov ya' tegen je zeggen, aangezien ik een gereserveerde Europese ben, doe ik dat niet. Maar de volgende keer dat Het Paard buitenkomt, gaan we samen kijken. Al reken ik er op dat het niet zo lang duurt voor ik iets van je hoor: je hebt mijn nummer, wanneer is de eerste lunch afspraak?

Andrea, ook jou wil ik heel graag bedanken, voor alle bemoedigende opmerkingen en de oprechte interesse in mijn af en toe wankelende gezondheidstoestand. Ze hebben deugd gedaan!

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Ik verlaat de universiteit en begin aan een heel nieuw leven, en ik weet dat ik daarbij kan rekenen op de steun van een aantal fantastische mensen!

Sabrina, Christel en Sofie, daar beland ik weer bij jullie... Jullie maakten de jaren aan De Overkant de moeite waard, en ik zou ze zo opnieuw doen als ik dan ook jullie weer mag leren kennen. Sabrina, jij verhuisde mee naar de Inwendige Ziekten, en ook al heb ik je de laatste maanden niet veel kunnen komen opzoeken daar beneden, zonder jou zou dit doctoraat nooit tot een goed einde zijn gebracht. Christel en Sofie, uit het Faculteitsoog, maar nooit uit het hart. Hou alvast jullie agenda's klaar, want ik ben van plan om al

bijeenkomsten vast te leggen voor de volgende twee jaar... Stefaan, Frank en Pieter, geen nood, jullie mogen vast wel eens ergens mee. Basketmatchke zien, iemand?

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Jullie waren er allemaal bij in Frankrijk – wat denken jullie, nieuwe afspraak juli 2015?

En dat brengt me bij jullie, lieve lieve familie. Een speciaal woordje gericht aan dokter Van Mulders: dankuwel voor alle logistieke en morele steun van de voorbije jaren. Het is ook dankzij u dat dit doctoraat er gekomen is. Al zal ik blij zijn dat de wekelijkse vraag 'Hoe gaat het met de thesis' nu niet meer gesteld zal worden... Aan mevrouw Van Mulders: dankuwel voor de culinaire ondersteuning, dankzij u eten we al jaren toch minstens één maal per week een warme maaltijd, maar bovenal voor de morele steun, subtieler, maar des te meer gewaardeerd. En natuurlijk een speciale vermelding voor een toekomstige peter, op verzoek: Pieter, je bent een schoonbroer uit de duizend!

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