Exercise-induced cardiac remodeling – a potential cause of pathological changes in the equine heart?

Träningsinducerad hjärtremodellering – en potentiell orsak till patologiska förändringar i hästens hjärta?

Maria Neil

Uppsala
2019

Exercise-induced cardiac remodeling – a potential cause of pathological changes in the equine heart?

Träningsinducerad hjärtremodellering – en potentiell orsak till patologiska förändringar i hästens hjärta?

Maria Neil

Handledare: *Elina Andersson & Fredrik Södersten, Sveriges lantbruksuniversitet, Institutionen för biomedicin och veterinär folkhälsovetenskap*

Examinator: *Maria Löfgren, Sveriges lantbruksuniversitet, Institutionen för biomedicin och veterinär folkhälsovetenskap*

TABLE OF CONTENTS

SUMMARY

Cardiac remodeling is a response to exercise that has been reported in a number of different species. Intensified training will lead to an increasing demand on the cardiovascular capacity, because of the requirements of enhanced oxygen delivery, metabolism and thermoregulation. An increased cardiac output is therefore needed, but it will only be able to change through an increased stroke volume as the maximal heart rate stays the same. An increased heart size is therefore the only way the animal can improve its cardiac capacity. Cardiac murmurs and valvular regurgitations may develop along with the enlargement of the heart. Whether these changes are physiological or pathological has been discussed.

This study aims to investigate how the equine heart responds to exercise, if cardiac remodeling can induce pathological changes in the heart and if upper airway obstructions can contribute to these pathological alterations.

An increased heart size can be seen after periods of intense exercise. This is caused by hypertrophy of the cardiomyocytes and, perhaps also, the formation of new cardiomyocytes from progenitor cells. The hypertrophy may lead to secondary pathological changes in terms of valvular regurgitations and arrhythmias. It seems like most valvular regurgitations occur due to leaking valves as the hypertrophy progresses. Arrhythmias can develop due to regurgitations and hypertrophy that effects areas important to the conducting system. Most arrhythmias, however, seem to be induced by imbalances in the autonomic nervous system, and may also occur as a result of exercise-induced changes in the heart through increased sensitivity to cholinergic stimulation. The most common cardiac causes of exercise intolerance in the horses seems to be mitral regurgitations and atrial fibrillation. Hypoxia associated with airway obstructions is a contributing factor to the cardiac remodeling as it causes a more excessive hypertrophy and potentially induces arrhythmias due to disturbances in the potassium homeostasis.

SAMMANFATTNING

Hjärtremodellering har rapporterats hos flertalet djurarter som ett svar på träning. Intensifierad träning leder till ökande krav på kardiovaskulär kapacitet, på grund av ökande behov av syretransport, metabolism och termoreglering. Detta ställer krav på ökad cardiac output, vilken kan förändras genom ökad slagvolym. Detta leder i sin tur till ökad hjärtstorlek och ökad hjärtkapacitet. Blåsljud och valvulära regurgitationer utvecklas ofta i samband med förstoringen av hjärtat, men om dessa förändringar är fysiologiska eller patologiska är omdiskuterat.

Den här studien syftar till att undersöka hur hästens hjärta svarar på träning, om hjärtremodellering kan leda till patologiska förändringar i hjärtat samt om luftvägsobstruktioner kan bidra till dessa förändringar.

Vid perioder av intensiv träning ses en ökad hjärtstorlek. Denna orsakas av hypertrofi av kardiomyocyterna samt, eventuellt också, bildandet av nya kardiomyocyter från progenitorceller. Hypertrofin kan sedan sekundärt leda till patologiska förändringar i form av valvulära regurgitationer och arytmier. De flesta valvulära regurgitationer förefaller uppstå på grund av läckande klaffar då hypertrofin fortskrider. Arytmier kan utvecklas på grund av valvulära regurgitationer eller hypertrofi som påverkar områden viktiga för retledningssystemet. De flesta arytmier verkar dock vara ett resultat av obalans mellan det sympatiska och parasympatiska nervsystemet, och kan också uppstå sekundärt till träning, genom ökad känslighet för kolinerg stimulering i hjärtat. De hjärtrelaterade problem som oftast orsakar nedsatt prestationsförmåga hos hästarna förefaller vara mitralisregurgitationer och förmaksflimmer. Hypoxi i samband med luftvägsobstruktioner är en bidragande faktor till träningsinducerad hjärtremodelleringen eftersom det kan orsaka överdriven hypertrofi och potentiellt framkalla förmaksflimmer på grund av en störd kaliumhomeostas.

INTRODUCTION

Exercise has been showed to imply cardiac remodeling and potentially induce pathological changes in the heart. As horses are bred for speed, congenital heart disorders are less common in horses than in other species (Weese, 2011). Despite this, a large number of our racehorses do present with different degrees of physiological and pathological murmurs (Patteson and Cripps, 1993) as well as arrhythmias (Buhl et al., 2013; Ryan et al., 2005). Cardiac hypertrophy has been shown as an adaption to training in both human athletes, racehorses, dogs and rodents (Kubo et al., 1974; Patteson and Cripps, 1993; Scharhag et al., 2002; Guasch et al., 2013, Stepien et al., 1998). Exercise-induced cardiac hypertrophy has in the horse been correlated to an increased incidence of murmurs and regurgitations, all this associated with periods of intense training rather than age (Kubo et al., 1974; Patteson and Cripps, 1993). Other factors contributing to potentially pathological changes in the hearts of our racehorses are airway obstructions, inflammatory episodes and perhaps, to some extent, heritability. Valvular regurgitations develops most commonly in the atrioventricular areas, both in the mitral and the tricuspid valves, but are not always audible by auscultation and may never get detected as they rarely affect performance (Kriz et al., 2000). If the regurgitations are physiological or pathological has been discussed. They have however been put forward as a potential cause of the development of arrhythmias and may have a role in events of sudden cardiac deaths.

This study aims to investigate how the equine heart responds to exercise and if cardiac remodeling can induce pathological changes in the heart. If so, what are the most common findings, how can we detect these changes and could upper airway obstruction be a contributing factor to the development of pathological changes?

MATERIAL OCH METHODS

The study was based on articles found in PubMed, Web of Science and Google Scholar. "Equine OR horse" where combined with the following words or phrases: "cardiac remodeling OR arrhythmia OR atrial fibrillation OR valvular regurgitation OR cardiorespiratory OR hypoxia".

A number of articles used where found through literature reviews on the subject. Veterinary cardiology textbooks were also used.

LITERATURE REVIEW

Circulatory system – anatomy and physiology

Anatomy

The heart consists of two atria and two ventricles. Deoxygenated blood from the body returns to the right atria (RA) and passes the right atrioventricular valve (tricuspid valve) to the right ventricle (RV). From the RV it passes through the right semilunar valve (pulmonary valve) out into the pulmonary artery and the lungs where the gas exchange takes place. Oxygenated blood then returns to the left atrium (LA) via the pulmonary veins. It passes through the left atrioventricular valve (mitral valve) to the left ventricle (LV) and finally through the left semilunar valve (aortic valve) to reach the aorta and the systemic circulation. From the base of the aorta two coronary arteries leaves to ensure blood support to the myocardium (Bright and Marr, 2010).

There are two types of myocardial cells – contractile and conductive cells. The conductive cells are an important part of the conductive system, specialized in spreading the electrical impulses through the heart in order to reach the contractile cells that are responsible for the contraction. Special nodal conductive cells are found in the sinoatrial (SA) and atrioventricular (AV) nodes. Conductive cells are also found in the bundle of His and the Purkinje system where conductive fibers are spread all the way through the ventricular walls to the epicardial surface. These cells are bigger than the cardiomyocytes and have the ability to transmit the electrical impulses in a much greater velocity which is essential for synchronized contraction of the thick ventricle walls (van Loon and Patteson, 2010).

Action potential

Action potential is generated spontaneously from the SA node, but also as a response to parasympathetic and sympathetic stimuli that alters heart rate and contractility. The electrical conductions are the sole cause of cardiac myocyte contraction. From the SA node the conduction spreads over the atrium to reach the AV node, thus, creates the electric potential that is seen as the P-wave on the electrocardiogram (ECG) (Fig. 1). The impulse conducts through the AV node where a delay influenced by autonomic tone determines the rate of further conduction. This is seen as the PR segment on the ECG (Fig. 1). Impulses then rapidly reaches over the bundle of His to the Purkinje system and reaches the myocytes in the ventricles. This is seen as the QRS-complex in the ECG. Ventricular repolarization, meaning returning of the myocytes to the resting phase, occurs without any stimuli. The repolarization is seen as the T wave on the ECG (Fig. 1) (van Loon and Patteson, 2010).
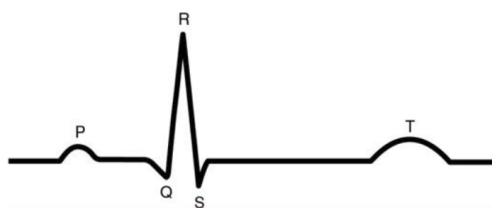

Figure 1 – ECG, a graph of voltage versus time showing the electrical activity of the heart, with the waves marked out (P-T). Modified from EKG-çerxa dillêdanê.png by https://openstax.org (CC BY 4.0).

Cardiac cycle

The QRS complex marks the beginning of ventricular systole. Electrical conduction from the AV node initiates depolarization of the ventricles, through the bundle of His and Purkinje system, and the cardiomyocytes start to contract. When the pressure in the left ventricle exceeds that of the aorta, the aortic valves open and blood flows out. Closing of the valves then marks the end of systole and ventricular diastole begins. Ventricular diastole is characterized by relaxation of myocytes, further decreasing the ventricular pressure until it reaches under the atrial pressure, allowing AV valves to open and fill the ventricles back up again. Duration of diastole varies with heart rate, being the longest at rest. Atrial systole, depolarization and contraction of the atria, is the last phase of the ventricular diastole and occurs just after the P wave (Bright and Marr, 2010; Irvine, 1975).

Equine cardiorespiratory capacity

In most mammals, and so also in the untrained horse, the heart generally makes up 0.6 % of the total bodyweight (Williams et al., 2015). The racehorse however has a much larger heart compared to its bodyweight as it makes up between 0.85 – 1 % (Gunn, 1989). A large heart facilitates a large stroke volume (the volume of blood leaving the ventricle every beat) and with a big variability in heart rate, ranging from 25 at rest to a maximum of 250 beats per minute, the cardiac output (the result of stroke volume and heart rate) can increase a lot in horses compared to most species. The maximal cardiac output can in trained horses during exercise reach over 300L/min - making the horse an excellent athlete (Bright and Marr, 2010). Splenic contraction induced by sympathetic activation is another feature of the horse that facilitates the delivery of oxygen to the tissues, making the hematocrit able to rise to nearly the double amount as what is seen in the resting horse (McKeever et al., 1993).

Aerobic exercise is dependent on oxygen delivery by blood to the muscle tissues. It is, therefore, the relationship between cardiac output and volume oxygen consumed per minute (VO_2) that determines the possible intensity of exercise (Liguzinski and Korzeniewski, 2007). VO_2 is determined by cardiac output (Q) and the arterial (aO_2) and venous (vO_2) oxygen difference.

$$VO_2 = Q * (aO_2 - vO_2)$$

In the horse both peak VO_2 and CO_2-output increase rapidly with intensified exercise and decreases in periods of detraining. When the level of exercise intensifies, the cardiovascular changes are mainly responsible for the increase in VO_2 as the ventilatory capacity has limited potential for adaptation (Art and Lekeux, 1993). Neither tidal volume (volume inspired or expired per breath), minute ventilation (volume inspired or expired per minute) or respiratory rate (breaths per minute) increase with training (Roberts et al., 1999). The limits to adaptation can partly be explained by the fact that respiration and step frequency is coupled in the galloping horse. This occurs at a 1:1 ratio, meaning that one breath is taken for every stride (Hornicke et al., 1987). Horses with different kinds of airway obstructions, such as dorsal displacement of the soft palate, fails to get a sufficient gas exchange which results in lower peak VO_2 and higher partial pressure of carbon dioxide ($PaCO_2$) (King et al., 1994; Tate et al., 1993). A milder form of exercise-induced hypoxemia is however present in all horses. This occurs at heavy exercise,

mostly as a result of limited oxygen diffusion between alveoli and capillaries, rather than the ventilation to perfusion ratio (Va/Q) mismatch seen in horses with airway problems (Wagner et al., 1989).

In a large international study on exercise related *post mortem* findings in racehorses, cardiac and/or pulmonary failure was shown to be the most common cause of sudden death, occurring in 29.9 % of the cases. In nearly as many cases, 25 %, the pathologists diagnosed the horses with presumptive cardiac or cardiopulmonary failure, as no gross lesions or histological findings could be seen. The cause of death remained completely unexplained in 21.6 % of the cases (Lyle et al., 2011).

Exercise-induced remodeling of the heart

Cardiac enlargement, caused by cardiomyocyte hypertrophy, is a response to exercise that has been shown in a large number of studies in different species. For example, exercise-induced cardiac hypertrophy in human athletes is a common finding, often referred to as "Athletes heart", where enlargement develops in a similar way in both LV and RV with increased muscle mass and increased ventricular internal dimensions (Scharhag et al., 2002). The same response has been seen in racehorses (Buhl et al., 2005; Kubo et al., 1974; Lightfoot et al., 2006; Young, 1999). Long term endurance exercise has been shown to induce cardiac hypertrophy in rats as well as mice (Guasch et al., 2013; Oláh et al., 2019; Radovits et al., 2013) and Alaskan sled dogs also present with a left sided hypertrophy after endurance training (Stepien et al., 1998).

Hypertrophy of the cardiomyocytes leads to an activation of cardiac progenitor cells that may be related to the increased levels of hepatocyte growth factor (HGF) and insulin like growth factor 1 (IGF-1) seen during long term exercise. The increased heart weight to body weight ratio may therefore be a result of both hypertrophy of the old cardiomyocytes and an addition of new cardiomyocytes (Xiao et al., 2014).

Increased LV mass has in horses been correlated to prolonged exercise as well as body weight. LV mass has also been showed to be greater in stallions than in mares (Buhl et al., 2005). The hypertrophy has been related to periods of intensified exercise rather than age (Kubo et al., 1974). Young *et al.* (1999) followed 2-year-old thoroughbred racehorses for 9 months, during this time the left ventricular mass increased with 33% and the left ventricular internal diameter increased with nearly 7 %. Buhl *et al.* (2005) showed a significant enlargement of the heart in standardbreds, 2-3.5 years of age, after intensified training. The horses were placed in two categories depending on recent training intensity, where the enlargement of the heart was shown to be greater in the high intensity training group. The horses presented with increased left ventricular diameter in diastole and increased left ventricular muscle mass. Buhl *et al.* did, in contrast to the study of Young *et al.*, not find an increase in relative wall thickness (RWT). An increased RWT indicates a shift towards a more concentric, rather than eccentric, hypertrophy (Katz et al., 2013).

Kubo *et al.* (1974) showed that cardiac enlargement occurs simultaneously in both ventricles in thoroughbred racehorses. RV internal dimensions are also increasing with training (Lightfoot et al., 2006).

Deconditioning after periods of intensive training results in decreased cardiac dimensions as well as a lower peak VO_2 after a period of time (Art and Lekeux, 1993; Kriz et al., 2000).

Upper airway obstruction – a contributing factor to pathological alterations in the heart?

Upper airway obstructions occur in horses in various degrees. The most common pathologies are dorsal displacement of the soft palate, palatal instability and laryngeal hemiplegia (Lane et al., 2006). A limited airflow at inspiration and, or, expiration leads to an impairment of the gas exchange (Franklin et al., 2002). This has been shown to get more severe with increased grades of laryngeal hemiplegia (Christley et al., 1997). At strenuous exercise the obstruction causes hypoxia, hypercapnia and in severe cases acidosis. The horse tires faster due to the lack of oxygen and the switch to anaerobic metabolism and may, in the long term, develop secondary cardiac changes. Another factor contributing to the limited oxygen uptake in some of these horses is the loss of locomotor-respiratory coupling, resulting in an abnormal breathing pattern where only one breath is taken over two strides (Fitzharris et al., 2014).

Hypertrophy of cardiomyocytes and perivascular fibrosis has been shown to develop as a response to intermittent hypoxia (Hayashi et al., 2018; Mitsuishi et al., 2019). A study made by Van Liere *et al.* (1964) showed that induced hypoxia creates a hypertrophy that is even greater than the one that develops solely after long term exercise. Cardiac remodeling and hypertrophy during hypoxia occurs due to an altered gene expression including activation of hypoxia inducible factor (HIF) and microRNAs called hypoxamiRs. The HIF1-α unit is under normal conditions suppressed by prolyl hydroxylase domain (PHD) enzymes, the activity of these enzymes is however inhibited during low oxygen levels. Activation of the HIF1-α transcription factors and hypoxamiRs leads to hypertrophy of cardiomyocytes and angiogenesis (Azzouzi et al., 2015).

Horses with upper airways obstructions may have more abnormal ECG findings than horses with clinically normal airways, most of these abnormal T-waves (Rose and Davis, 1978). Myocardial affection that result in changed ventricular repolarization leads to abnormal T-waves. While Rosie and Davis (1978) related the abnormal T-waves to poor performance, Evans (1991) pointed on the fact that they occur in a big proportion of the horses, thus, suggesting it may be a normal response to training. The prevalence of abnormal T-waves was however, in the study by Rosie and Davis (1978), higher in poor performance horses and in horses with upper airway obstructions.

Upper airway obstruction in horses entails a risk for the development of arrhythmias, not only caused by excessive hypertrophy but also due to the changes in the potassium homoeostasis. The hypercapnia can, together with buildup of lactate from working muscles, result in a lowered blood pH and thereby acidosis. The lowered pH may, through increased plasma potassium

levels, lead to hyperkalemia. The rise in plasma potassium levels can disturb the heart function by affecting the membrane potential, and can lead to arrhythmias seen as ventricular tachycardia (multiple consecutive ventricular premature complexes on the ECG) or atrial fibrillation (Maxson-Sage et al., 1998; Tate et al., 1993; Young et al., 1954).

Clinical findings

Murmurs and regurgitations
Valvular regurgitations seems to be the most common acquired heart disease in horses (Vitale et al., 2012). The regurgitations occur because of physiological or pathological changes to the heart valves, resulting in changes of the hemodynamic flow that creates regurgitant jets (Marr, 2010). The frequency of murmurs and regurgitations seems to increase with time in training and probably corresponds to the increased heart size (Buhl et al., 2005; Reef et al., 2014; Young et al., 2008). It has also been showed that racehorses are more affected than pleasure horses (Patteson and Cripps, 1993). When valvular regurgitations are present, cardiac murmurs can sometimes be detected at clinical examination as the turbulence in blood flow creates a sound. Regurgitant jets can, with a color flow Doppler ultrasound, be detected in most racehorses even if they are clinically normal on heart auscultation as these are not always audible as murmurs (Marr and Reef, 1995). Regurgitations do not always involve structural changes of the heart valves. In physiological conditions, exercise-induced hypertrophy will lead to a leakage from the valves, while in pathological conditions, hypertrophy will be secondary to insufficient valves (Decloedt et al., 2014). Physiological regurgitations has not been associated with impaired racing performance (Young et al., 2008).

The number of racehorses affected with valvular regurgitations varies between 80-90 % in studies, depending on examination methods (Buhl et al., 2013; Marr and Reef, 1995; Young, 1999; Young et al., 2008). Mitral regurgitations (MR) in racehorses are to the most part mild and physiological (Young et al., 2008). More severe cases can lead to exercise intolerance, ventricular arrhythmias and atrial fibrillation (AF). MR may develop due to exercise-induced hypertrophy and dilation of the LV, or secondary to aortic insufficiency that also creates a LV hypertrophy. Insufficiency of the mitral valves can lead to regurgitation of blood into the atria and therefore an increased size of the LA and, thus, development of atrial fibrillation. Tricuspid regurgitations (TR) are along with MR the most common types of regurgitations found in racehorses. Development of TR may occur due to dilation and hypertrophy of the RV, induced by training and an altered cardiac load, or secondary to pulmonary hypertension. TR are less prone to induce dysrhythmias than other valvular insufficiencies and are rarely itself associated with poor performance. Aortic regurgitations (AR) are not as common as the atrioventricular ones in racehorses, as they more commonly develop in older horses. Low degree regurgitations usually do not affect performance. Severe cases with larger jets are however a bigger issue and can be associated with ventricular dysrhythmias (Kvart and Häggström, 2002; Marr, 2010).

Arrhythmias
Arrhythmias occur due to a large number of cardiac diseases and can be detected as abnormal findings on the ECG. Exercise-induced causes of arrhythmias are valvular regurgitations as

well as dysrhythmias induced by hypoxia and changes in autonomic tone (Reef and Marr, 2010). It has therefore been suggested that ventricular hypertrophy can trigger arrhythmias in horses (Kriz et al., 2000; Pedersen et al., 2013) . In humans, long term exercise has been associated with higher risk of developing both atrial and ventricular arrhythmias (Andersen et al., 2013). Abnormal ECG patterns has been reported to occur in as much as 60 % of human athletes (Pelliccia Antonio et al., 2000).

A prolonged QT interval has in humans been associated with the development of arrhythmias and sudden cardiac death (Haugaa *et al.*, 2014). In human and small animals, the prolongation occurs when the electrical conductions take longer time to spread through a thickened myocardium after exercise-induced remodeling. The depolarization of the ventricles in horses does however not occur in a similar way and it has therefore been suggested that a prolonged QT interval can not be used to estimate ventricular size (van Loon and Patteson, 2010). QT intervals in horses has, despite this, been showed to be longer in stallions than in mares (Pedersen *et al.*, 2013).

Supraventricular premature complexes (SVPC) are dysrhythmias caused by premature contractions of the atria. Premature atrial beats result in abnormal P-waves. SVPCs are of concern as they can cause atrial fibrillation (Binici Zeynep et al., 2010). Ventricular premature complexes (VPC) are dysrhythmias caused by premature contractions of the ventricles and results in premature QRS complexes. Repeatable VPCs can result in ventricular tachycardia (Kiryu et al., 1999). A study showed that premature complexes, both VPCs and SVPCs, in horses were associated with higher heartrates at peak exercise (Ryan et al., 2005). Premature complexes may also develop due to electrolyte imbalance (Leroux et al., 1995; Maxson-Sage et al., 1998). Buhl *et al.* (2013) studied the development of SVPC and VPC to assess associations between cardiac hypertrophy, valvular regurgitations and arrhythmias. In their study, the number of SPVC were lower after training while VPC increased. Ryan *et al.* (2005) showed a higher number of both VPC and SVPC post exercise as well as in warm up. These findings were probably related to the change in autonomic tone as there was no significant associations between heart size and arrhythmias (Buhl et al., 2013; Ryan et al., 2005).

Changes in autonomic tone, both sympathetic and parasympathetic activation, have frequently been associated with different kinds of arrhythmias. Activation of the sympathetic system and increased levels of circulating catecholamines can be an inciting cause of atrial fibrillation (Carnagarin et al., 2019). Parasympathetic activation, on the other hand, can also lead to arrhythmias. A study that Guasch *et al.* (2013) performed on rats showed that after exercise-induced cardiac remodeling, the rats appeared to be more susceptible to atrial fibrillation with an increased sensitivity to cholinergic stimulation in cardiomyocytes, probably due to downregulation of some of the regulator of G-protein signaling (RGS) proteins. RGS constitutes a family of proteins that modulates the cardiac autonomic responses. RGS4 is one of the proteins that was downregulated in the study. Higher levels of RGS4 has been found in the SA node compared to the within the right atrium. RGS4 plays an important inhibiting role in parasympathetic signaling and therefore also in alterations of the sinus rhythm (Cifelli et al., 2008; Guasch et al., 2013).

Heritability has also been suggested as a factor contributing to the development of atrial fibrillation in standardbreds (Physick-Sheard et al., 2014).

Cardiac troponin I

Cardiac troponin (cTnI) is a well-known biomarker for myocardial damage in both humans and horses. Reference levels of cTnI have been described in normal horses (Phillips et al., 2003). Elevated levels of cTnI can in horses be used to detect myocardial disease while other cardiac diseases, such as structural lesions and arrhythmias, rarely result in increased cTnI levels (Nath et al., 2012). cTnI has also been shown to increase mildly 10-14 hours post-race in horses without other signs of cardiac disease (Nostell and Häggström, 2008).

DISCUSSION

Cardiac hypertrophy has been shown to increase with intensified training (Buhl et al., 2005; Reef et al., 2014; Young et al., 2008). The hypertrophy is induced by alterations in cardiac load and can also lead to formation of new cardiomyocytes from progenitor cells (Xiao et al., 2014). There is however, in my opinion, a lack of control groups in most studies. I think it is an important aspect as most studies have been done on young, still growing, horses. It would be valuable to know how the heart in the young, untrained horse develops to get more comparable measures than only pre/post periods of exercise. As the hypertrophy, and therefore heart size, decreases with ceased training it is no doubt that a correlation between heart size and exercise exists (Kriz et al., 2000). The lack of studies on the right ventricle of the heart is probably due to the limited possibility to measure the right ventricle with ultrasound (Young et al., 2006) but it is likely that the right ventricle responds to training in a similar way as the left just as in human athletes (Scharhag et al., 2002). The relative wall thickness seems to differ between thoroughbreds (Young et al., 1999) and standardbreds (Buhl et al., 2005), a finding that I think may be explained by the dissimilar work that these horses perform.

Valvular regurgitations and cardiac murmurs are consistently reported as a response to the cardiac enlargement occurring with exercise (Kubo et al., 1974; Patteson and Cripps, 1993). Most of the regurgitations are however in such a low grade as they cannot be considered as clinically relevant (Young et al., 2008). Mild to moderate valvular regurgitations are not considered a big problem in young horses if they do not occur at different valves simultaneously or if the horses show no other clinical signs or present with poor performance (Marr, 2010). A color flow Doppler would therefore be necessary to clinically assess the number and severity of regurgitations (Marr and Reef, 1995). With this method it may be possible to distinguish physiological cardiac remodeling from the hypertrophy that occurs due to a primary valve disease.

The development of exercise-induced hypoxia during training may contribute to the cardiac remodeling. Upper airway obstructions should be of concern as they can induce a more severe cardiac remodeling with impact on cardiac function, both by hypoxia-induced hypertrophy and perivascular fibrosis (Hayashi et al., 2018; Mitsuishi et al., 2019; Van Liere et al., 1965). Acidosis in these horses should also be considered as a risk factor for the development of arrhythmias due to increased plasma potassium levels (Maxson-Sage et al., 1998). I think it should be remembered that these horses, while racing, usually pull up fairly quickly at the onset of obstruction. The hypoxia may therefore not get as severe as in studies where it has been induced (Hayashi et al., 2018; Mitsuishi et al., 2019). Repeatable occurrences, and the onset of obstructions in more severe cases while exercising even at lower speeds, may still be enough to induce secondary cardiac changes. The abnormal breathing pattern seen in some of these horses may also be contributing.

Abnormal T-waves as a response to myocardial dysfunction have been related to poor performance in some studies (Rose and Davis, 1978) while others have pointed on the fact that they occur in a big proportion of the horses, thus, suggesting it may be a normal response to

training (Evans, 1991). Rose and Davis showed that abnormal T-waves where a much more common finding in groups of poor performance horses and horses with upper respiratory tract abnormalities. Mildly increased cTnI levels after racing may, according to the authors Nostell & Häggström (2008), be related to the low degrees of hypoxia that occurs in all horses during strenuous exercise, creating a leakage of cTnI from cardiomyocytes without inducing degeneration. In the study made by Nostell & Häggström (2008), the cTnI levels post racing were mildly increased, but still well below levels that Phillips *et al.,* (2003) considered as normal. The lack of a significant increase in cTnI after racing suggest that a lot of the exercise-induced changes occur without myocardial degeneration. This applies to both arrhythmias and valvular regurgitations as the cTnI levels are not elevated in most of these cases (Nath et al., 2012).

It seems like an imbalance between sympathetic and parasympathetic nervous system rather than any structural changes causes the high occurrence of arrhythmias. Downregulation of RGS protein in conjunction with intense exercise may contribute to this, as a sensitization to cholinergic stimuli could affect the balance between sympathetic and parasympathetic nervous system and thereby potentially induce an increased risk for arrhythmias (Guasch *et al.,* 2013). While these studies are based on rats, I think it would be of interest to see further studies on exercise and the downregulation of RGS protein and if this could apply to the horses as well. Atrial fibrillation that develops during a race or strenuous exercise is often paroxysmal and spontaneous conversion usually occurs within 48 hours and can, thus, only be detected the following day at the latest (Reef and Marr, 2010). This may have affected the very low prevalence of horses presenting with AF in studies. Other underlying causes such as heritability has been suggested to increase the risk of atrial fibrillation, but more studies would be needed as the cause of the development of AF in these horses is not clear (Physick-Sheard et al., 2014).

In conclusion, cardiac hypertrophy is a natural response to training. The increase of regurgitations and heart murmurs are correlated to the enlargement and probably occurs due to stretching of the valves that creates a leakage. They are to the most part mild and physiological without any impact on performance. Most arrhythmias are induced by the changes in autonomic tone and occurs both pre-, during and post-exercise. Mitral regurgitations and atrial fibrillation seem to be the most common cardiac causes of exercise-related poor performance. Upper airway obstructions can cause an excessive, hypoxia-induced hypertrophy and induce arrhythmias due to disturbances in the potassium homeostasis. Many exercise-induced changes of the heart seem to occur without any structural changes. I think that arrhythmias may, because of the lack of histological changes and gross lesions, be a reasonable explanation for some of the unexplained or presumptive cardiac deaths on the racetracks and respiratory obstruction a predisposing factor for these. Further studies would be needed to develop new methods to assess equine heart function and predict these events.

REFERENCES

Andersen, K., Farahmand, B., Ahlbom, A., Held, C., Ljunghall, S., Michaëlsson, K., Sundström, J., (2013). Risk of arrhythmias in 52 755 long-distance cross-country skiers: a cohort study. *Eur. Heart J.* 34, 3624–3631.

Art, T., Lekeux, P., (1993). Training-induced modifications in cardiorespiratory and ventilatory measurements in Thoroughbred horses. *Equine Vet. J.* 25, 532–536.

Azzouzi, H. el, Leptidis, S., Doevendans, P.A., Windt, L.J.D., (2015). HypoxamiRs: regulators of cardiac hypoxia and energy metabolism. *Trends Endocrinol. Metab.* 26, 502–508.

Binici Zeynep, Intzilakis Theodoros, Nielsen Olav Wendelboe, Køber Lars, Sajadieh Ahmad, (2010). Excessive Supraventricular Ectopic Activity and Increased Risk of Atrial Fibrillation and Stroke. *Circulation* 121, 1904–1911.

Bright, J.M., Marr, C.M., 2010. Chapter 1 - Introduction to cardiac anatomy and physiology, in: Marr, C.M., Bowen, I.M. (Eds.), *Cardiology of the Horse (Second Edition)*. Edinburgh: W.B. Saunders, 3–19.

Buhl, R., Ersbøll, A.K., Eriksen, L., Koch, J., (2005). Changes over time in echocardiographic measurements in young Standardbred racehorses undergoing training and racing and association with racing performance. *J. Am. Vet. Med. Assoc.* 226, 1881–1887.

Buhl, R., Petersen, E.E., Lindholm, M., Bak, L., Nostell, K., (2013). Cardiac Arrhythmias in Standardbreds During and After Racing—Possible Association Between Heart Size, Valvular Regurgitations, and Arrhythmias. *J. Equine Vet. Sci.* 33, 590–596.

Carnagarin, R., Kiuchi, M.G., Ho, J.K., Matthews, V.B., Schlaich, M.P., (2019). Sympathetic Nervous System Activation and Its Modulation: Role in Atrial Fibrillation. *Front. Neurosci.* 12, 1058.

Christley, R.M., Hodgson, D.R., Evans, D.L., Rose, R.J., (1997). Cardiorespiratory responses to exercise in horses with different grades of idiopathic laryngeal hemiplegia. *Equine Vet. J.* 29, 6–10.

Cifelli Carlo, Rose Robert A., Zhang Hangjun, Voigtlaender-Bolz Julia, Bolz Steffen-Sebastian, Backx Peter H., Heximer Scott P., (2008). RGS4 Regulates Parasympathetic Signaling and Heart Rate Control in the Sinoatrial Node. *Circ. Res.* 103, 527–535.

Decloedt, A., Ven, S., Vekens, N.V.D., Clercq, D.D., Loon, G. van, (2014). Differentiating Pathological from Physiological Left Ventricular Hypertrophy by Quantifying Myocardial Function. *Equine Vet. J.* 46, 21–21.

Evans, D.L., (1991). T-waves in the equine electrocardiogram: Effects of training and implications of race performance. *Equine Exerc. Physiol.* 3, 475–481.

Fitzharris, L., Franklin, S., Allen, K., (2014). The Prevalence of Abnormal Breathing Patterns During Exercise and Associations with Dynamic Upper Respiratory Tract Obstructions. *Equine Vet. J.* 46, 22–22.

Franklin, S.H., Naylor, J.R.J., Lane, J.G., (2002). Effect of dorsal displacement of the soft palate on ventilation and airflow during high-intensity exercise. *Equine Vet. J.* 34, 379–383.

Guasch, E., Benito, B., Qi, X., Cifelli, C., Naud, P., Shi, Y., Mighiu, A., Tardif, J.-C., Tadevosyan, A., Chen, Y., Gillis, M.-A., Iwasaki, Y.-K., Dobrev, D., Mont, L., Heximer, S., Nattel, S., (2013). Atrial Fibrillation Promotion by Endurance Exercise: Demonstration and Mechanistic Exploration in an Animal Model. *J. Am. Coll. Cardiol.* 62, 68–77.

Gunn, H.M., 1989. Heart weight and running ability. J. Anat. 167, 225–233.

Hackett, R.P., Ducharme, N.G., Gleed, R.D., Mitchell, L., Soderholm, L.V., Erickson, B.K., Erb, H.N., (2003). Do Thoroughbred and Standardbred horses have similar increases in pulmonary vascular pressures during exertion? *Can. J. Vet. Res.* 67, 291–296.

Haugaa, K.H., Bos, J.M., Borkenhagen, E.J., Tarrell, R.F., Morlan, B.W., Caraballo, P.J., Ackerman, M.J., (2014). Impact of left ventricular hypertrophy on QT prolongation and associated mortality. *Heart Rhythm* 11, 1957–1965.

Hayashi, T., Sasaki, M., Watanabe, A., Furukawa, Y., Nomura, A., Uehashi, W., Kato, R., Ijiri, Y., Nakagawa, T., Asahi, M., Yamaguchi, T., Izumi, Y., Yoshiyama, M., (2018). O-Linked N-Acetyl Glucosamine (o-Glcnac) Regulates Autophagy and Apoptosis in Cardiomyocytes: A Double-Edged Sword in Intermittent Hypoxia-Induced Cardiac Remodeling. *J. Am. Coll. Cardiol.* 63, A868.

Hornicke, H., Weber, M., Schweiker, W., 1987. Pulmonary ventilation in Thoroughbred horses at maximum performance. In: J.R. Gillespie and N.E. Robinson (eds.), *Equine Exercise Physiology II,* Davic, CA: ICEEP Publications, 216–224

Irvine, C.H.G., (1975). Electrocardiographic anomalies in the racehorse. *N. Z. Vet. J.* 23, 262–269.

Katz, D., Beussink, L., Sauer, A., Freed, B., Burke, M., Shah, S., (2013). Prevalence, Clinical Characteristics, and Outcomes Associated With Eccentric Versus Concentric Left Ventricular Hypertrophy in Heart Failure With Preserved Ejection Fraction. *American journal of cardiology*, 112, 1158-1164.

King, C.M., Evans, D.L., Rose, R.J., (1994). Cardiorespiratory and metabolic responses to exercise in horses with various abnormalities of the upper respiratory tract. *Equine Vet. J.* 26, 220–225.

Kiryu, K., Machida, N., Kashida, Y., Yoshihara, T., Amada, A., Yamamoto, T., (1999). Pathologic and electrocardiographic findings in sudden cardiac death in racehorses. *J. Vet. Med. Sci.* 61, 921–928.

Kriz, N.G., Hodgson, D.R., Rose, R.J., (2000). Changes in cardiac dimensions and indices of cardiac function during deconditioning in horses. *Am. J. Vet. Res.* 61, 1553–1560.

Kubo, K., Senta, T., Sugimoto, O., (1974). Relationship between Training and Heart in the Thoroughbred Racehorse. *Exp. Rep. Equine Health Lab.* 1974, 87–93.

Kvart, C., Häggström, J., (2002). Cardiac auscultation and phonocardiography. Uppsala.

Lane, J.G., Bladon, B., Little, D.R.M., Naylor, J.R.J., Franklin, S.H., (2006). Dynamic obstructions of the equine upper respiratory tract. Part 1: Observations during high-speed treadmill endoscopy of 600 Thoroughbred racehorses. *Equine Vet. J.* 38, 393–399.

Leroux, A., Schott, H., Hines, M., (1995). Ventricular-Tachycardia Associated with Exhaustive Exercise in a Horse. *J. Am. Vet. Med. Assoc.* 207, 335–337.

Lightfoot, G., Jose-Cunilleras, E., Rogers, K., Newton, J.R., Young, L.E., (2006). An echocardiographic and auscultation study of right heart responses to training in young National Hunt Thoroughbred horses. *Equine Vet. J.* 38, 153–158.

Liguzinski, P., Korzeniewski, B., (2007). Oxygen delivery by blood determines the maximal V O 2 and work rate during whole body exercise in humans: in silico studies. *Am. J. Physiol.-Heart Circ. Physiol.* 293, H343–H353.

Lyle, C.H., Uzal, F.A., Mcgorum, B.C., Aida, H., Blissitt, K.J., Case, J.T., Charles, J.T., Gardner, I., Horadagoda, N., Kusano, K., Lam, K., Pack, J.D., Parkin, T.D., Slocombe, R.F., Stewart, B.D., Boden, L.A., (2011). Sudden death in racing Thoroughbred horses: An international multicentre study of post mortem findings. *Equine Vet. J.* 43, 324–331.

Marr, C.M., (2010). Chapter 16 - Cardiac murmurs: valvular regurgitation and insufficiency, in: Marr, C.M., Bowen, I.M. (Eds.), *Cardiology of the Horse (Second Edition)*. Edinburgh: W.B. Saunders, 207–216.

Marr, C.M., Reef, V.B., (1995). Physiological valvular regurgitation in clinically normal young racehorses: prevalence and two-dimensional colour flow Doppler echocardiographic characteristics. *Equine Vet. J.* 27, 56–62.

Maxson-Sage, A., Parente, E.J., Beech, J., Lindborg, S., May, L.L., Teleis, D.C., (1998). Effect of high-intensity exercise on arterial blood gas tensions and upper airway and cardiac function in clinically normal Quarter Horses and horses heterozygous and homozygous for hyperkalemic periodic paralysis. *Am. J. Vet. Res.* 59, 615–618.

McKeever, K.H., Hinchcliff, K.W., Reed, S.M., Robertson, J.T., (1993). Role of decreased plasma volume in hematocrit alterations during incremental treadmill exercise in horses. *Am. J. Physiol.-Regul. Integr. Comp. Physiol.* 265, R404–R408.

Mitsuishi, R., Imano, H., Kato, R., Ijiri, Y., Yamaguchi, T., Yoshiyama, M., Hayashi, T., (2019). Rivaroxaban Attenuates Cardiac Remodeling Due to Intermittent Hypoxia by Suppressing the Synergistic Effects of Par-1 and Par-2. *J. Am. Coll. Cardiol.* 69, 2033.

Nath, L.C., Anderson, G.A., Hinchcliff, K.W., Savage, C.J., (2012). Serum cardiac troponin I concentrations in horses with cardiac disease. *Australian Vet. J.* 90, 351-357.

Nostell, K., Häggström, J., (2008). Resting concentrations of cardiac troponin I in fit horses and effect of racing. *J. Vet. Cardiol.* 10, 105–109.

Oláh, A., Kovács, A., Lux, Á., Tokodi, M., Braun, S., Lakatos, B.K., Mátyás, C., Kellermayer, D., Ruppert, M., Sayour, A.A., Barta, B.A., Merkely, B., Radovits, T., (2019). Characterization of the dynamic changes in left ventricular morphology and function induced by exercise training and detraining. *Int. J. Cardiol.* 277, 178–185.

Patteson, M.W., Cripps, P.J., (1993). A survey of cardiac auscultatory findings in horses. *Equine Vet. J.* 25, 409–415.

Pedersen, P.J., Kanters, J.K., Buhl, R., Klaerke, D.A., (2013). Normal electrocardiographic QT interval in race-fit Standardbred horses at rest and its rate dependence during exercise. *J. Vet. Cardiol.* 15, 23–31.

Pelliccia Antonio, Maron Barry J., Culasso Franco, Di Paolo Fernando M., Spataro Antonio, Biffi Alessandro, Caselli Giovanni, Piovano Paola, (2000). Clinical Significance of Abnormal Electrocardiographic Patterns in Trained Athletes. *Circulation* 102, 278–284.

Physick-Sheard, P., Kraus, M., Basrur, P., McGurrin, K., Kenney, D., Schenkel, F., (2014). Breed predisposition and heritability of atrial fibrillation in the Standardbred horse: A retrospective case–control study. *J. Vet. Cardiol.* 16, 173–184.

Radovits, T., Oláh, A., Lux, Á., Németh, B.T., Hidi, L., Birtalan, E., Kellermayer, D., Mátyás, C., Szabó, G., Merkely, B., (2013). Rat model of exercise-induced cardiac hypertrophy: hemodynamic characterization using left ventricular pressure-volume analysis. *Am. J. Physiol.-Heart Circ. Physiol.* 305, H124–H134.

Reef, V.B., Bonagura, J., Buhl, R., McGurrin, M.K.J., Schwarzwald, C.C., Loon, G. van, Young, L.E., (2014). Recommendations for Management of Equine Athletes with Cardiovascular Abnormalities. *J. Vet. Intern. Med.* 28, 749–761.

Reef, V.B., Marr, C.M., (2010). Chapter 13 - Dysrhythmias: assessment and medical management, in: Marr, C.M., Bowen, I.M. (Eds.), *Cardiology of the Horse (Second Edition)*. Edinburgh: W.B. Saunders, 159–178.

Philips, W Philips, W, Giguere, S, Franklin, RP, et al., (2003). Cardiac troponin I in pastured and race-training thoroughbred horses. *J. Vet. Intern. Med.* 17, 597–599

Roberts, C.A., Marlin, D.J., Lekaux, P., (199). The effects of training on ventilation and blood gases in exercising Thoroughbreds, *Equine Vet. J.* 31, 57–61.

Rose, R.J., Davis, P.E., (1978). The use of electrocardiography in the diagnosis of poor performance in the horse. *Aust. Vet. J.* 54, 51–56.

Ryan, N., Marr, C.M., McGladdery, A.J., (2005). Survey of cardiac arrhythmias during submaximal and maximal exercise in thoroughbred racehorses. *Equine Vet. J.* 37, 265–268.

Scharhag, J., Schneider, G., Urhausen, A., Rochette, V., Kramann, B., Kindermann, W., (2002). Athlete's heart: Right and left ventricular mass and function in male endurance athletes and untrained individuals determined by magnetic resonance imaging. *J. Am. Coll. Cardiol.* 40, 1856–1863.

Stepien, R.L., Hinchcliff, K.W., Constable, P.D., Olson, J., (1998). Effect of endurance training on cardiac morphology in Alaskan sled dogs. *J. Appl. Physiol.* 84, 1368–1375.

Tate, L.P., Corbett, W.T., Bishop, B.J., Foreman, J.H., (1993). Blood Gas Tensions, Acid-base Status, Heart Rates, and Venous Profiles in Exercising Horses with Laryngeal Hemiplegia Before and After Corrective Surgery. *Vet. Surg.* 22, 177–183.

Van Liere, E.J., Krames, B.B., Northup, D.W., (1965). Differences in Cardiac Hypertrophy in Exercise and in Hypoxia. *Circ. Res.* 16, 244–248.

van Loon, G., Patteson, M., 2010. Chapter 6 - Electrophysiology and arrhythmogenesis, in: Marr, C.M., Bowen, I.M. (Eds.), *Cardiology of the Horse (Second Edition).*, Edinburgh: W.B. Saunders, 59–73.

Vitale, V., Sgorbini, M., Caivano, D., Birettoni, F., Giorgi, M.E., Tognetti, R., Porciello, F., (2012). Valvular insufficiency in the horse: personal observations (2005-2011). *Ippologia* 23, 3–8.

Wagner, P.D., Gillespie, J.R., Landgren, G.L., Fedde, M.R., Jones, B.W., DeBowes, R.M., Pieschl, R.L., Erickson, H.H., (1989). Mechanism of exercise-induced hypoxemia in horses. *J. Appl. Physiol.* 66, 1227–1233.

Weese, S., (2011). Equine Clinical Medicine, Surgery and Reproduction. Boca Raton: CRC Press.

Williams, T.M., Bengtson, P., Steller, D.L., Croll, D.A., Davis, R.W., (2015). The Healthy Heart: Lessons from Nature's Elite Athletes. *Physiology* 30, 349–357.

Xiao, J., Xu, T., Li, J., Xu, J., Lv, D., Chen, P., Zhou, Q., (2014). Exercise-induced physiological hypertrophy initiates activation of cardiac progenitor cells. *Int. J. Clin. Exp. Pathol.* 7, 663–669.

Young, L.E., (1999). Cardiac responses to training in 2-year-old thoroughbreds: an echocardiographic study. *Equine Vet. J.* Suppl. 195–198.

Young, L.E., Helwegen, M.M.G.H.J., Rogers, K., Kearns, L., Schreiber, C., Wood, J.L.N., (2006). Associations between exercise-induced pulmonary haemorrhage, right ventricular dimensions and atrioventricular valve regurgitation in conditioned National Hunt racehorses. *Equine Vet. J.* 38, 193–197.

Young, L.E., Rogers, K., Wood, J.L.N., (2008). Heart Murmurs and Valvular Regurgitation in Thoroughbred Racehorses: Epidemiology and Associations with Athletic Performance. *J. Vet. Intern. Med.* 22, 418–426.

Young, W.G., Sealy, W.C., Harris, J.S., (1954). The role of intracellular and extracellular electrolytes in the cardiac arrhythmias produced by prolonged hypercapnia. *Surgery* 36, 636–649.