Insight in cardiac patients of a referral clinic:
valvular regurgitations: will they become clinically relevant?

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Abstract

A retrospective observational study among equine cardiac patients is performed including 603 horses. The study concentrated on the general characteristics, diagnoses and clinical relevance of the equine cardiac patients and the long-term prognosis for valvular regurgitations. The 603 horses included 60.0% geldings, 28.7% mares and 11.3 % stallions. Warmblood horses were with 76.8% the most prevalent breed and 69.5% of the studied population was 10 years of age or younger. In 586 horses an echocardiography was performed. Valvular regurgitations were with 55.3% the most frequent diagnosed condition, followed by horses with only flow murmurs or no abnormality found at all in 15.6% of cases. Valvular regurgitations combined with arrhythmias were diagnosed in 9.3% of horses, arrhythmia's alone in 6.1%, the diagnosis of myocarditis, endocarditis and pericarditis together in 4.6%, congenital abnormalities in 4.0%, aneurysms in 0.7%, and other diagnoses in 4.3%. In 11.9% of the 603 horses the cardiac condition was considered to be clinical relevant at the time of examination. For the evaluation of the long-term prognosis for valvular regurgitations, information is gained from 125 horses. The mean time between first examination and the follow-up was $6,7 \pm 2,7$ year (2,7-14,4) and consisted of 22 horses with small regurgitations, 60 with moderate and 43 with severe valvular regurgitations. The mean age of the horses at first examination was $9,9 \pm 5,4$ years $(2,4-26,0)$. From the 125 horses 72 were kept in ownership while 30 had died or were euthanized for various reasons in between the examination and follow-up. In three horses signs of heart failure was present at the time of euthanasia according to the owner. From the 42 horses that were alive, 32 were in various uses as riding or breeding horses and the other 10 horses were retired. In none of these 42 horses did the owner reported clinical signs of cardiac failure in the horse under the current circumstances. If a horse with valvular regurgitations were to start showing signs of cardiac failure, it seems that a diagnosis of moderate or severe regurgitation must be accompanied by several other abnormalities including severely enlarged cardiac chambers or arrhythmias and this will likely take years. Clear signs of cardiac disease did not seem to show up in the 42 horses in an average of 6.5 years following the first diagnosis. How many years these horses can eventually cope with their cardiac condition and under what circumstances remains uncertain and should be further investigated.

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Introduction

Cardiac murmurs and arrhythmias are often found during clinical examination of horses and they can be an indication of serious cardiac disease that is likely to limit the athletic ability of the horse and its future career (Reef 1987, Reef 1998, Hall, Magdesian & Kittleson 2010, Deem, Fregin 1982). However murmurs and arrhythmias are common in horses without any symptoms of disease or perceived loss of performance (Patteson, Cripps 1993, Reef 1993, Buhl, Meldgaard & Barbesgaard 2010, Slack et al. 2015). It is the task of the equine practioner to differentiate between abnormalities that are no threat to the performance of the horse at the moment of examination and in the future and the ones that are. The future evolutions of cardiac abnormalities in equines are sometimes difficult to predict and may not be a problem for many years but at times can progress rapidly* (Gehlen 2007b). Because of this,

abnormal cardiac findings can potentially lead to disagreements in sales, judicial affairs and claims.

Endocarditis, myocarditis, pericarditis, aneurysms and congenital abnormalities can be a cause for the clinical finding of heart murmurs, arrhythmias or both and are likely clinical relevant. (Briceño 2015, Hall et al. 2010, Jesty, Reef 2006, Maxson, Reef 1997, Worth, Reef 1998). Reported prevalence's of congenital cardiac abnormalities are low with around 0.1-0.5% of horses affected. Ventricle septum defects are the most common congenital abnormality (Hall et al. 2010). The prevalence of myocarditis, endocarditis, pericarditis and aortic aneurysm are low (Maxson, Reef 1997, Briceño 2015).

Hypoxia, septicemia, endotoxemia, endocrine or metabolic disturbances and structural abnormalities can all be a cause for the initiation of pathologic arrhythmias in horses (Reef, Bowen & Marr 2010, Reef et al. 2014). Arrhythmias that disappear after exercise, like sinus arrhythmias, 2nd degree AV-block or SA-block and even some single ventricular or supraventricular extrasystole (VES, SVES) are

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* Author observation, this happened in patients with file number: 1004460, 905313 and 1308656.

considered to be physiological (Reef et al. 2010, Reef et al. 2014). Multiple VES or SVES, followed by each other can be a sign for the development of ventricle tachycardia, atrial tachycardia, complex ventricle arrhythmias or atrial fibrillation (AF). These pathological arrhythmias can be a reason for loss of performance, exercise intolerance, collapse and sudden death (Deem, Fregin 1982, Navas de Solis 2016, Reef et al. 2014).

The most important, pathological arrhythmia for sport horses is AF, followed by SVES and VES (Gehlen 2007a, Martin Jr 2000, Deem, Fregin 1982). In a study using all horses offered for further diagnosis in an equine clinic facility, the prevalence of AF was 0.06 - 0.63%, sometimes AF was an incidental finding (Deem, Fregin 1982). In racehorses, the prevalence of AF after a race was 0.11% and even 2% if the horse raced poorly (Slack et al. 2015).

The prevalence of cardiac murmurs found differs among studies ranging from 21 to 68% in a large group of horses from different breeds and purposes (Stevens et al. 2009, Patteson, Cripps 1993, Leroux 2013) to 80% in well performing racehorses (Marr, Reef 1995). The breed, use and stage of training are related to the prevalence of cardiac murmurs (Wijnberg et al. 2014, Patteson, Cripps 1993). A common cause of cardiac murmurs is valvular regurgitation. Valvular regurgitation is very common in horses even if no murmurs can be heard (Blissitt 1995). Color flow Doppler is a very sensitive technique to detect regurgitations, and it's prevalence in normal horses ranges from 40 to 80% (Blissitt 1995, Marr 1995). The difference between physiological and pathological regurgitations can be a point of discussion, and is partly dependent on the criteria used as the study of Blissitt, 1995 discusses. Athletic training is known to increase the prevalence of valvular regurgitation in all valves, but especially in the tricuspid valve (Buhl 2012, Wijnberg et al. 2014, L. E. Young 2000, Buhl 2005). In the study of Buhl, 2005 the severity of the training-induced regurgitations remained the same over a 1,5 year study period and was classified as being mild in all valves it was observed. Exercise immediately before echocardiography and sedatives alter the prevalence of regurgitations, be it for only a short duration (Buhl 2006, Buhl 2007).

The functioning of the valve is dependent upon several components and anything that affects their functionality could cause regurgitation, but valvular distortion seems to be a common cause, especially in severe cases. (Reef 1998, Davis 2002). In horses with severe mitral regurgitation with symptoms of CHF, valve abnormalities where found in 84% of horses. Thickening of the valve was with 79% the most prevalent abnormality. (Reef 1998). Also among horses without a history of cardiac dysfunction are valvular lesions widespread and in a large study among 1557 slaughter horses of different breed and ages 28,7% of all horses had cardiac lesions, with 80% being valvular (Else, Holmes 1972). The etiology of the valvular distortion is likely to be related to age, physical trauma, infection or a combination of these factors, but most of them are degenerative in nature. (ELSE 1972).

Most valvular regurgitations are of minimal consequence on the performance in sport horses; in a longitudinal epidemiological study of the association between cardiac valvular regurgitations and racing performance, no consistent association was found (L. E. Young, Rogers & Wood 2008). Even years after the initial diagnosis, many horses with valvular regurgitation are doing well. In a follow-up study of horses diagnosed with valvular regurgitation, 73% were still in use in the same way after the initial diagnosis, in 20% the demands were reduced or the horse was pulled back of competitive sports and in 7% the horse was not ridden anymore (Gehlen 2007a). The follow-up time was 2-11 years, but no distinction is made between time of follow up, the outcome and the severity of the regurgitation. In the study from Stevens et al, 2009 horses with a left sided regurgitation did not have a higher mortality rate than other horses (Stevens et al. 2009).

Deterioration of the regurgitation seems to occur slowly and the severity of mitral regurgitation did not progress in a 2-9 year period from mild to moderate or severe in a study in 108 horses, although the left ventricle did increase in size (Imhasly 2010). This enlargement is also recorded in the study from Gehlen et all, 2007 were left sided regurgitation resulted in a significant enlargement of the ventricle, atrium or both over the years. (Gehlen 2007b) But only a small number of animals did show a noticeable deterioration clinically as well as on echocardiography. In some instances valvular regurgitation and in particular mitral and aortic regurgitation did result in congestive heart failure and death (L. Young 2007, Reef 1998, Gehlen 2007a). Many horses with congestive heart failure or poor performance attributed to cardiac disease did not have valvular regurgitation alone, but suffered from myocardial disease, congenital abnormalities, endocarditis, ruptured chorda tendinae or pathological arrhythmias as well (Reef 1998, Martin Jr 2000, Davis 2002) (L. Young 2007).

This study concentrates upon the equine cardiac patients admitted at the department of equine health, faculty of veterinary medicine, Utrecht. Gives an overview of the general characteristics, diagnosis and clinical significance of the equine cardiac patients and the long-term prognosis of horses with valvular regurgitations.

Materials and methods
Patients:

Horses admitted at the Faculty of Veterinary Medicine, department of equine health between 2006-2016 were reviewed if their files included an

echocardiography or ECG or at least a circulatory consultation. The following criteria were used to include or exclude the files that were delivered to the author:

- Animals must be horses
- Echocardiography performed: file included
- Separate ECG performed: file included except when the ECG is performed for educational purposes.
- Patients with a cardiac diagnosis without further diagnostics are only included if a circulatory consult was present in the file.

If an animal was admitted more than once between 2006-2016 the initial file is used for the documentation of the general characteristics. Horses that were reexamined between 2006 and 2016 but had their first examination before 2006 were included in the study and the data of the first visit is used. No distinction is made between horses that were referred for a circulatory examination alone or horses that were already hospitalized and in which the ECG or echocardiography was part of their workup. For each animal the following details were recorded:

- Examination date
- Breed, sex, date of birth
- Reasons for consultation
- Diagnosis
- Clinical significance of the cardiac disease at time of first examination
- Characteristics of valvular insufficiencies if present:
  o Severity of valve that showed the most severe regurgitation
  o Number and kind of valves that showed regurgitation
- Cardiac measurements if present:
  o LA (cm)
  o LVID(d) (cm)

Definitions:
Diagnosis: Because several different cardiac findings were often present in one horse, the following rules were used to assign the patients to one particular group:

- Valvular regurgitations and arrhythmias were inferior to congenital abnormalities, myocarditis, endocarditis, pericarditis and aneurysms.
- If a definite diagnose of endocarditis, myocarditis or pericarditis could not be made for whatever reason, but was suspected by the attending clinician and written down in the *"letter to the owner"* or in the communication part of the file, it was regarded as such. Interpretation of outcomes from diagnostic tests was avoided as much as possible.

- Because arrhythmias were seen frequently during echocardiography, pathological arrhythmias are always documented and no distinction is made between arrhythmias that were diagnosed during echocardiography or with a separate ECG

For the classification of the diagnoses, distinction was made between horses that received an echocardiography and those that did not. The following classification of diagnoses were made in horses that received an echocardiography:

- Valvular regurgitation: horses were assigned to this group if the echocardiography showed signs of valvular regurgitation. The classification is unrelated to the presence or absence of a cardiac murmur.
- Arrhythmia: horses diagnosed with a VES, SVES, AF or other potentially pathological arrhythmias were assigned to this group. No regurgitations are seen on echocardiography. Horses with obvious physiological arrhythmias like 2nd degree AV-block, SA-block or sinusarrhythmia are excluded. No distinction is made between physiological occurring VES or SVES. The patient files often did not contain clear information in this regard to make this discrimination without interpretation from the author. Also, no distinction is made between solitary or multiple occurring VES or SVES or time of occurrence as in many files the information was incomplete in this regard.
- Valvular regurgitations and arrhythmia: horses diagnosed with a VES, SVES, AF or other potentially pathological arrhythmias in combination with valvular regurgitations as determined during echocardiography were part of this group.
- Endocarditis, myocarditis or pericarditis: horses that received a likely diagnosis of endocarditis, myocarditis and or pericarditis were part of this group. The likely diagnosis had to be mentioned in the "*letter to the owner*" or communication part of the file.
- Congenital abnormality: horses with a diagnosis of a congenital abnormality. No horses with a diagnosis of congenital abnormalities in combination with myocarditis, endocarditis or pericarditis or a combination of congenital abnormality and aneurysms were present in this study.
- Aneurysm or aortic rupture: horses diagnosed with an aortic aneurysm, ante mortem or post mortem.
- No regurgitation or arrhythmia: horses in this group did not have regurgitation on echocardiography and VES, SVES, AF or other potentially pathological arrhythmias. Many did have a cardiac murmur, but the presence or absence of it was not used in the classification.

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- Other: some horses could not be classified in one of the above groups mostly because of lack of data available in the patient file or an incomplete performed echocardiography.

In the horses that did not receive an echocardiography, information from an ECG, physical examination or port mortem were used to determine the diagnosis. The following classifications were made:

- Arrhythmia: horses diagnosed with a VES, SVES, AF or other potentially pathological arrhythmias were assigned to this group.
- No pathological arrhythmia: this group consists of horses with an obvious physiological arrhythmia like 2nd degree AV-block, SA-block or sinusarrhythmia, or horses without any arrhythmia present during examination at the clinic.

Clinical significance: The patients were considered to have a clinical significant cardiac disease when the cardiac diagnosis was regarded as the cause of the symptoms of disease or loss of performance. This is documented in the file in the communication part or in the " *letter to the owner*" mostly accompanied by findings of elevated heart rates during telemetric exercise, gross cardiac chamber enlargements, severe regurgitations or pathological arrhythmia's. In some instances the clinical significance of the diagnosis could not be determined with certainty, because:

- Further diagnostic test should be performed to determine the significance of a diagnosis
- The horse had several secondary health issues (lameness, respiratory disease) which could all be responsible for the clinical signs of disease or loss of performance
- Lack of information available in the file

In these instances, the cardiac condition was not regarded as clinical significant in the results.
The horses diagnosed with endocarditis, pericarditis, myocarditis or aneurysm were always regarded as clinical significant cardiac disease, even if the diagnosis was not accompanied by disease or complaints of loss of performance.
Severity of regurgitation: for determining the severity of the regurgitations, the written description of the severity in the radiological report of the file was used. The jet measurements were not used to determine the severity of the regurgitation.

Follow-up

The initial question for this thesis was to investigate which equine cardiac patients were at risk for developing clinical relevant cardiac disease. However, because the selection for follow-up by telephone would become too extended for an investigation of 3-month duration and the number of reexaminations for the different diagnoses to small and biased to be useful for this part, it was decided to concentrate only on horses diagnosed with valvular regurgitations. The reason for choosing horses with valvular regurgitation was that this group made up the majority of cardiac patients admitted to the clinic. Also, first line veterinarians will most likely be confronted about questions regarding cardiac murmurs and because valvular regurgitations are an important cause of murmurs, long-term prognosis of valvular regurgitations are of interest more so than other cardiac diseases.

Selection:
All animals of the 603 horses were included in follow-up if they were diagnosed with:

1. Moderate to severe valvular regurgitations with or without an arrhythmia
2. Did not have a clinical significant cardiac disease at the time of first consultation
3. Were examined for the first time before 2015.
4. Horses with small regurgitations are included if their LVID(d) measured more then 12,5 cm and/or their LA measured more then 13,5 cm.

Because mild valvular regurgitations have a favorable prognosis and even horses with moderate to severe regurgitations seem to cope with their cardiac condition for some years, the aim of this selection was to gather enough patients that would have developed clinical significant cardiac disease to determine risk factors for the prediction of the prognosis. Because dilatation of cardiac chambers are considered in formulating a prognosis, horses with mild regurgitations are included of their LVID (d) was larger then the reference size of 12,5 cm and the atrium larger then 13,5cm. It is known that not all horses that fitted these criteria were having cardiac dilation.

Table 1: Owners questionnaire

Is the horse kept in ownership?

Yes:
 • Is the horse still alive?
    • If not: when did the horse die, how and what is the cause of death or euthanasia?
    • Did the horse show any cardiac related symptoms of disease before death?
 • Is the horse in use as a riding horse?
 • At what level is the horse exercised? *
 • Does the horse show any cardiac related symptoms of disease according to the owner?

No: • When is the horse sold?   • Did the horse show any signs of cardiac related disease before it was sold?   • Is the horse still alive?   • Is the horse in use as a riding horse?   • At what level is the horse exercised?

* The level of exercise is divided in:
1. Very light riding: mainly short walks, very little trotting or cantering
2. Recreational riding or low-level competition (B – M)
3. High-level competition (Z – international)

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Owner interview:

The follow up is executed by telephone to inquire details regarding ownership, current use of the horse and presence of any cardiac related symptoms. If the horse was euthanized or had died, the reason and date was asked as well as if the cardiac condition was related to the cause of death. In case the horse was sold, any information is used that the previous owner could tell. The questionnaire that was used can be viewed in table 1. In 7 cases the owner was not contacted anymore, because it was known that the horse had died or was euthanized or the horse was reexamined in 2017. Details in the patient file were used in these cases, the rest of the follow-up contained only owner based subjective information; no objectified information was available from the owner's feedback.

Use of reexaminations:

A few horses that are selected for follow-up were reexamined at the clinic between the first examination and follow-up. Information from the last reexamination was used to gather information of the state of cardiac measurements in relation to the first examination.

Statistical analyses

The results from the follow-up did not allow a regression analysis to be performed because the number of horses that did develop clear cardiac failure was too small. This is discussed with dr. J van den Broek. The use of a general linear model is discussed to be able to tell more about the predictive value of the age of the horse, kind of valve that showed a regurgitation and number of regurgitations that were present in regard to the LA and LVID(d) size. It was decided not to use it, because of the complexity of the model and the fact that it was not in line with the questions in this study. To include statistical analysis and to present the findings of the cardiac measurements, it was decided to compare the mean LA and LVID(d) size between horses with non, mild, moderate and severe regurgitation. Because LA and LVID(d) size is known to be associated with body weight to a certain extent, a selection of horses is made to be able to compare the cardiac measurements. The horses had to be:

- Warmblood horses, 3 years and older
- Have a diagnosis *"valvular regurgitation"* or *"no regurgitation or arrhythmia"*

Horses from other diagnosis are excluded because the condition could influence the results. The number of horses available for analysis were N= 295 for LA size and N=281 for LVID(d). In some patient files, only the measurement of LA or LVID(d) was available for documentation, which explains the different number. SPSS, version 24 is used for statistical analyses to compare the means of the LA and LVID(d) measurements of the divers groups of horses. One-way ANOVA is used in combination with Bonferroni post-hoc correction test. The independent samples T-test is used for the comparison of mean LA size and mean LVID(d) size between horses with mitral and aortic valve regurgitation. Significance was set at $P \leq 0.05$.

Results

In total 603 horses met the inclusion criteria and were reviewed. In 586 horses an echocardiography was performed. Between 2006 and 2016, 76 horses were reexamined at least once more in that time frame, 56 of these 76 horses were diagnosed with only valvular regurgitations at the first examination. Only 13 horses were admitted for the first time before 2006 and reexamined between 2006 and 2016.

The patients consisted of 60.0% geldings, 28.7% mares and 11.3 % stallions. The number of new horses that were admitted each year fluctuated from a minimum of 35 in 2012 to 71 in 2013. Breeds from many different studbooks were present and were classified in table 2. The vast majority of horses, 76.8% consisted of warmblood breeds. Details of age can be found in table 3, it was notable that 69.5% of horse were ten years of age or younger at the time of consultation.

Most horses, 68.3% did not have any signs of disease and sales examinations and abnormal cardiac auscultation during a routine clinical examination made up the main reason for consulting the clinic. In 0.9% the patient file lacked information about existing signs of disease and 30.8% of horses examined did show various clinical signs of disease. The most common being a general loss of performance, sometimes accompanied by loss of weight, lethargy, fever, respiratory symptoms, edema and other signs of disease. Fainting or collapse is reported nine times. The classical signs of congestive heart failure with ventral edema and respiratory signs were rare and only present in five cases for certain. In 68 of the 186 horses assessed due to symptoms of disease, the symptoms were attributed to the cardiac diagnosis. In 10 horses from the 186 the cardiac condition might be the cause for clinical signs of disease but the information in the patient files was inconclusive in these instances.

Table 2: Different breeds

Breed	N
Warmblood	463
Thoroughbred	35
Friesian	26
Pony	8
Trotters	9
Draft type	9
Quarter horse	8
Unknown	45

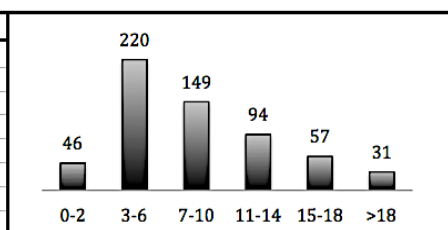Table 3: Age of the horse in years at first examination

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Table 4: Diagnoses and clinical relevance of the cardiac findings

Diagnosis	N	Murmur present	Valvular regurgitation present	Clinically relevant cases
Echocardiography performed:				
Valvular regurgitation	334	327	334	4
Arrhythmias	24	5	0	6
Valvular regurgitation and arrhythmia	56	40	56	21
Myocarditis, endocarditis or pericarditis	28	14	17	28
Congenital abnormality	23	22	14	7
Aneurysm or aortic rupture	4	4	1	4
No regurgitation or arrhythmia	94	87	0	0
Other	5	2	-	0
Total	**568**	**501**	**422**	**70**
No echocardiography:				
Arrhythmias	13	4	-	1
Congenital abnormality	1	1	-	1
No pathological arrhythmia	21	2	-	0
Total	**35**	**8**	**-**	**2**

Diagnoses and clinical relevance
In 72 horses or 11.9% the cardiac condition was considered to induce signs of disease or exercise intolerance in the horse at the time of consultation. In 4 of these 72 horses the owner did not perceive any signs of disease. In table 4 details of the diagnoses and number of horses with clinically significance disease for each diagnosis was summarized.
In 87 of the 94 horses from the group *no valvular regurgitation or arrhythmia*, a cardiac murmur was heard and flow murmurs were the cause of the cardiac murmurs in these horses. Thus 87 horses out of 603, or 14.4% of all horses that were admitted at the clinic were having solely flow murmurs. Determination of the source of the cardiac murmurs was not part of this study however and the real number of horses with flow murmurs from the 603 horses could not be stated.
The 80 horses from the group *echocardiography performed: arrhythmia* and *valvular regurgitation and arrhythmia*, 66.3% suffered AF, followed by VES in 22.5% of these 80 horses. SVES were seen in four horses, atrial fluttering in three, sinustachycardia in five horses, atrial premature complexes in one horse, AV-dissociation in one and high grade SA-block in one horse as well. Combinations of different arrhythmias were present in six horses. From the 13 horses from the group *no echocardiography: arrhythmia*, six were diagnosed with AF, two with VES, three with SVES and two with atrial premature complexes.

From the 21 horses from the group *no echocardiography: no pathological arrhythmia*, nine are diagnosed with a 2nd degree AV-block, seven with sinus arrhythmia and in five no arrhythmias were found.
In 8 from the 28 horses from the group *myocarditis, endocarditis or pericarditis*, a post mortem examination was performed. The diagnosis of myocarditis was confirmed in five horses. The diagnosis of endocarditis was confirmed in four horses. One horse had confirmed pericarditis. Two of these eight horses had a combination of endocarditis or pericarditis with myocarditis. From the other 20 horses, 17 were diagnosed with myocarditis. From these 17 horses, 16 had arrhythmias and the one without arrhythmia a severely diminished fractional shortening of 11%. From the 11 horses tested for cardiac enzymes, in 10 they were elevated. From the other three horses out of 20, two are diagnosed with endocarditis and one with pericarditis.
Ventricle septum defect was with 75% the most prevalent congenital abnormality, followed by a persistent ductus of Botalli with 12.2%. The Tetralogy of Failot was present once, one horse had a ventricle septum defect together with an exchange of the aorta and the pulmonary artery and one horse was presented with an aortopulmonary window. In one horse no echocardiography is performed and the diagnosis was confirmed by post mortem examination. All horses diagnosed with an aneurysm were Friesians.

Table 5: Measurements of LVID

	N	Mean + SD (cm)	Range (cm)
No regurgitation	50	11,2 ± 1,46	8,3 − 13,9
Mild regurgitation	134	11,5 ± 1,39	7,8 − 15,2
Moderate regurgitation	58	12,1a ± 1,09	9,8 − 14,5
Severe regurgitation	39	13,5a ± 2,27	8,5 − 18,4

a. Significant difference, P≤ 0,005 in mean between all other means. One-way Anova, post hoc: Bonferroni.

Table 6: Measurements of LA

	N	Mean +SD (cm)	Range (cm)
No regurgitation	53	12,4 ± 0,95	10,4 − 14,8
Mild regurgitation	140	12,5 ± 0,98	10,0 − 15,1
Moderate regurgitation	61	12,9 ± 0,99	10,2 − 15,3
Severe regurgitation	41	13,5a ± 1,40	11,0 − 17,2

a. Significant difference, P≤ 0,005 between mean of severe regurgitation and all other means. One- way Anova, post hoc: Bonferroni

From the 334 horses diagnosed with valvular regurgitation from the group *Echocardiography performed: valvular regurgitation,* mitral regurgitation was most prevalent with 67,7% followed by aortic regurgitation with 50,3%, tricuspid regurgitation 44.0% and pulmonary regurgitation with 6,6%. From the same group of 334 horses 56.3% had a mild regurgitation, 23.4% had a moderate regurgitation and 18.3% had a severe regurgitation.

Regurgitation in only one valve was present in 48.5% out of 334 horses, 36.8% had regurgitation in two valves, 12.3% in three valves and 2,4% in all four valves. In 22 horses valve abnormalities were witnessed and included valve prolapse and thickening of the valves. A thickened papillary muscle was found once.

In table 5 the mean of the left ventricle internal diameter during diastole (LVID) can be viewed and in table 6 the size of left atrium for different groups of horses. No significant differences were found in average LVID (d) and LA between the horses with mild regurgitations and horses without regurgitations, but both horses with moderate and severe regurgitations showed significant larger cardiac chambers. For LVID (d) no significant difference is found in mean between horses mitral regurgitations and aortic regurgitations, P= 0,869. But for mean LA size, mitral regurgitation showed a significant larger mean, p= 0,039.

Follow-up

For the follow-up 148 horses met the inclusion criteria described in the section materials and methods and were included. Information was received from 125 horses. The mean follow-up period of the 125 horses was 6,7 ± 2,7 year (2,7-14,4) and consisted of 22 horses with small regurgitations, 60 with moderate regurgitation and 43 with severe valvular regurgitation. The mean age of the horses at first examination was 9,9 ± 5,4 years (2,4 – 26,0). Seven of the 125 horses were having arrhythmias at time of first examination at the clinic; five had AF, one atrial fluttering and one VES after exercise. An overview of the follow-up can be viewed in figure 1.

Horses kept in ownership: causes of death
In the time between first examination and follow-up, 30 horses had died. From these 30 horses, 26 were euthanized for various reasons, see figure 1. In three of these 26 horses symptoms of cardiac decompensation was present before death according to the owner and in one of these congestive heart failure is confirmed by echocardiography at a clinic, following euthanasia. AF was diagnosed in two of these three horses at the first examination. The four horses that were not euthanized all died while in turnout. None of these horses were examined post mortem and the reason behind the death is unexplained. From these four horses one had a dilated aorta measuring 9 cm, two others were diagnosed with AF besides the regurgitation. One of these horses was reexamined one year after the initial
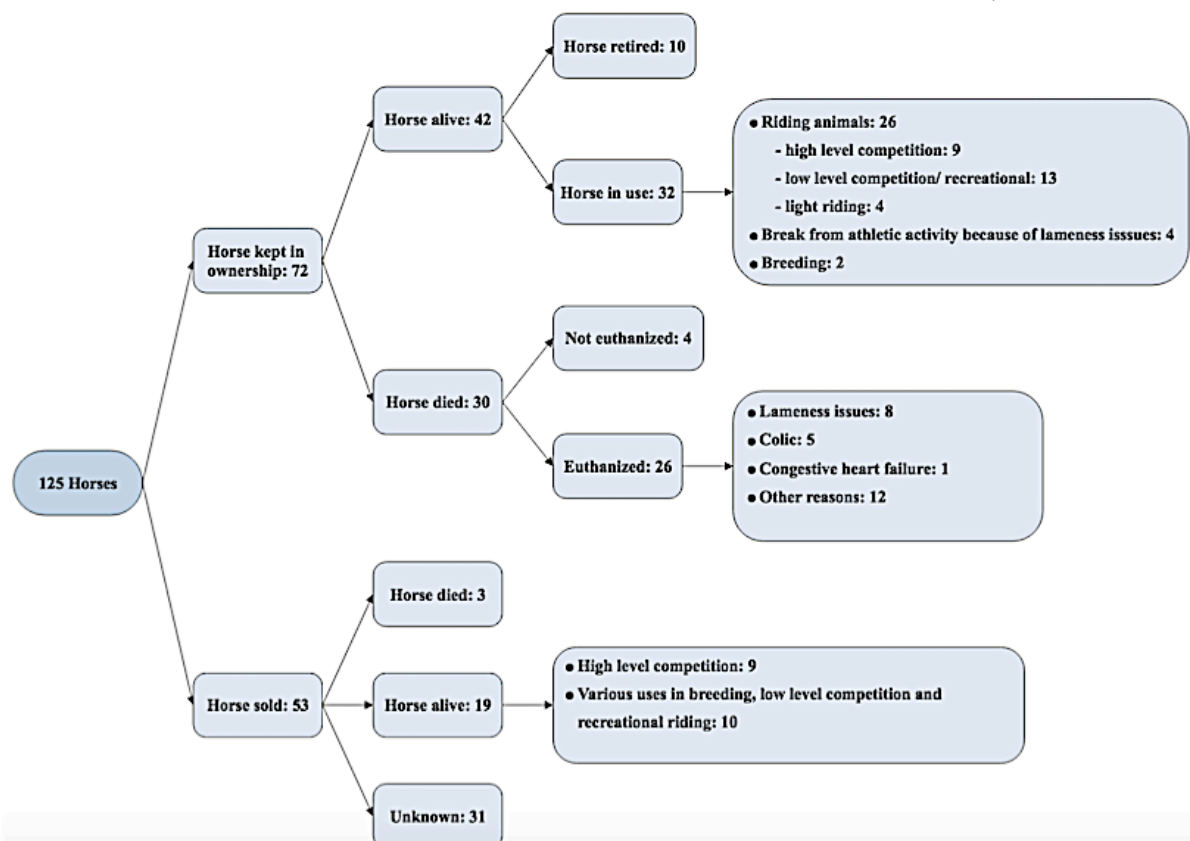

Figure 1: Results of follow-up

Table 7: Details of different groups of horses after follow-up

	N	Mean age at examination	Follow-up time (years)	Mean LVID (d) (cm)	Mean LA (cm)	Severity and valve of most severe regurgitation*
Kept in ownership:						
High competition horses	9	6,4 ± 3,2	6,03 ± 2,5	12,6 ±1,1	13,3 ± 1,2	3: LAV – mod/ sev 2: AO- sev 1: PA – sev 2: LAV - mild
Recreational/ Low level competition	13	10,5 ± 5,5	6,1 ± 3,2	12,2 ± 1,3	13,2 ± 0,9	2: LAV – mod 2: AO – mod 4: RAV – mod/ sev 5: RAV/LAV/AO -mild
Light recreational	4	14,0 ± 5,7	8,7 ± 2,8	13,8 ± 1,1	12,8 ± 0,6	1: LAV- sev 3: AO- sev
Breeding horses	2	5,6 ± 1,1	6,2 ± 1,0	12,7 ± 1,8	13,1 ± 1,7	2: LAV- mod/ sev
Horses with lameness issues	4	5,2 ± 2,4	4,3 ± 1,0	13,0 ± 1,6	13,2 ± 0,6	3: LAV- mod 1: AO - sev
Retired horses	10	14,1 ± 3,5	8,1 ± 2,7	12,9 ± 1,3	12,8 ± 0,6	1: LAV – sev 3: AO – mod/sev 4: RAV – mod/sev 2: AO - mild
Horses euthanized with symptoms of cardiac failure or found dead	7	15,5 ± 4,0	4,8 ± 3,5**	14,3 ± 1,8	14,7 ± 1,3	4: LAV – mod/ sev 2: AO - mod/ sev 1: RAV – mod
Horses sold:						
High competition horses	9	9,1 ± 3,6	5,9 ± 2,5	12,0 ± 1,8	12,7 ± 1,1	4: LAV – mod/sev 2: AO – mod 3: RAV mild/mod
Recreational riding and other purposes	10	9,4 ± 4,1	5,8 ± 2,9	12,9 ± 1,4	13,3 ± 0,9	5: LAV – mod/ sev 2: AO – mod/sev 2: LAV – mild 1: AO - mild

* Mild, moderate (mod) or severe (sev) regurgitations.

**The follow up time in these horses are from first examination till death.

diagnosis, and echocardiography showed no deterioration. Details of age, follow-up time, cardiac measurements and severity of the valve that showed the most severe regurgitation are summed up in table 7 for different groups of horses.

Horses kept in ownership: use of the horse
In figure 1 the different uses can be viewed from the 32 horses that were kept in ownership and were in use at the time of follow-up. The two horses that were used for breeding have done very well in sports, working in high level competition and are not pulled back because of the cardiac condition.
Nine from the 26 horses were working at high competition level; at least six of them were used in active competition in jumping and dressage classes. All are doing well without any loss of performance according to the owner. Four of these horses were reexamined at the clinic between 0.5 and 7 years. The cardiac measurements remained stable in all these horses, but in two of them small regurgitations at other valves were visible.
From the 26 riding horses, 13 were working at lower level competition or used for recreational riding. In a few horses the demands were reduced because of age or non-cardiac related health issues. Eight horses were reexamined at the clinic, mostly 1 to 3 years after the initial examination, but two horses had 6 and 10 years in between examinations. The measurements of LVID(d) and LA remained constant in all horses, but one horse with moderate aorta regurgitation showed a larger regurgitant jet.
Four from the 26 horses were only used for very light riding purposes at time of follow-up, mainly short rides at a walk with little trotting or cantering. In three of these horses, the overall body condition and endurance capacities were reduced according to the owner. If this was related to compromised cardiac function is not known. In two of them reexamination took place 3 and 11 years after the first examination. On one horse the measurements were the same, in the other which was diagnosed with severe mitral regurgitation, only mild regurgitations could be found after reexamination.

Horses kept in ownership: retired horses
None of the 10 horses that were retired had symptoms of cardiac failure and all except one is retired because of problems with fitness that might be related to the heart. This horse was an internationally 160 km endurance racer and didn't recover fast enough to continue at this level. That same horse was reexamined three years after the initial diagnoses with deteriorating cardiac LVID(d) an LA sizes, but is doing fine 11.5 years after the first examination. One other horse with severe tricuspid regurgitation is reexamined one year after the first diagnosis and no valvular regurgitations could be found at that time. Two owners reported that their horse was deteriorated in general health and athletic ability, but if this is directly related to the cardiac condition is not clear.

Horses sold:
Between the first examinations and follow-up, 52 horses were sold. In 19 cases the previous owner followed the horse and could tell that the horse was doing well. Nine of them are working at high-level

competition. The other 10 horses had various uses in recreational riding, low-level competition and breeding. In three cases, the horse has died; one because of colic and two of unknown cause.

Discussion

In this study, 603 horses were available for retrospective analysis. Most horses were referred without signs of disease, endorsing the widespread prevalence of cardiac arrhythmias and murmurs among horses without clinical cardiac disease (Stevens et al. 2009, Reef 1995, Buhl et al. 2010, Barbesgaard, Buhl & Meldgaard 2010, Imhasly 2010, Gehlen 2007a). They also indicate that coincidental cardiac findings are an important reason for owners to perform further diagnostics and that these were deemed necessary by the referring vet to be able to tell the significance of the clinical findings.

An interesting result was the high number of horses, 14.4% of the studied population with cardiac murmurs but diagnosed without regurgitations or arrhythmia's and thus with functional flow murmurs. It does indicate the difficulty for the referring vet to discriminate between murmurs caused by pathological valvular regurgitation and physiological flow murmurs, or that owners or veterinarians wanted more assurance in the light of a sales examination. If the diagnosis could be made with only auscultation, the horse would probably not get referred to the clinic for an echocardiography. The total number of flow murmurs present among the 603 horses was probably with 14.4% even an underestimation. Because 56.3% of the 334 horses that were diagnosed with *valvular regurgitations* had only mild regurgitations and some of them might not be the cause of the cardiac murmur heard during auscultation as several studies reported the presence of regurgitations without associated murmurs (L. E. Young 2000, Buhl 2005, Marr 1995).

The group of 334 horses diagnosed with *valvular regurgitations* made up more than half the diagnoses, namely 55.3%. The distribution of regurgitations found per valve with mitral and aortic regurgitations being the most prevalent were similar to the results found in the study of (Gehlen 2007a) in a likewise population of horses. However, they were different from the findings in other studies in other populations in which tricuspid regurgitations were the most prevalent (Marr 1995, L. E. Young 2000, Buhl 2005). The horses in these studies were active or recently retired racehorses or trotters and in the studies from Young, 200 and Marr, 1995 selected to be without clinical signs and without a history of cardiovascular disease. Because tricuspid regurgitation is rarely associated with clinical signs (Reef 1995) and can be training induced (Buhl 2012, Wijnberg et al. 2014, L. E. Young 2000, Buhl 2005), this might be the reason for the discrepancy found between the prevalence of the different valve

regurgitations as these horses are not referred by the veterinarian. The low occurrence of pulmonary valve regurgitation in this study is however peculiar. Small regurgitant jets at the pulmonary valve are common in horses (Blissitt 1995, Marr 1995) and the occurrence of pulmonary regurgitation is probably underestimated in this study.

Horses with clinically relevant cardiac disease consisted of 11.9% of the studied population at the time of first consultation. This percentage might not be totally accurate. Because the information is gathered retrospectively and the results from the diagnostics performed not interpreted as much as possible, the relevancy of the cardiac condition had to be stated clearly in the communication part of the file or in the " *letter to the owner"* to be classified as being so. This was not always the case for various reasons, sometimes the files were missing information, or further diagnostics should be performed in order to make an accurate decision about the clinical relevancy of the condition. Horses with a diagnosis of myocarditis, endocarditis, pericarditis or aneurism were always considered clinical relevant in this study, perhaps incorrectly, in contrary to diagnosis of congenital abnormalities, arrhythmia's and valvular regurgitations. The diagnosis of myocarditis, endocarditis and pericarditis were unfortunately not straightforward in every case and there was doubt about the accuracy of the diagnosis in 5 to 10 cases. If the diagnosis was mentioned as likely in the " *letter to the owner"* or communication part of the file, it was regarded as such, but in some patient files only little information was available or it was stated that the diagnosis was not completely certain. In a few cases, no more then about five that were not regarded as suffering from myocarditis or endocarditis, cardiac enzymes were elevated, valvular distortions present or the horse had likely pathological arrhythmia's, but no mention in the file about the possibility of myocarditis or endocarditis. If these files would be reviewed by the clinician that had written it or by a cardiologist, perhaps some alterations were made in the number of horses assigned per diagnosis and with that its clinical relevance. The vast majority of cases however could be accurately assigned without much doubt using the criteria set out in the materials and methods section.

The result of the follow-up, which includes horses with severe regurgitations at different valves, clearly underlines the reasonable good prognosis for horses with valvular regurgitation, which is in line with earlier studies (Imhasly 2010, Gehlen 2007b, Stevens et al. 2009). The four horses that are found dead and the three that are euthanized with signs of heart failure according to the owner were put together in one group in table 7, as horses that might have died with cardiac failure. The mean age of these horses and both their mean LVID(d) and LA size were the highest of all groups. While their follow-up time till

death is among the lowest of all. Four from these seven horses were diagnosed with AF as well during the first examination. While in total, only seven horses from follow-up had an arrhythmia. This result points out that high age, severe regurgitations, severe cardiac chamber dilatation in combination with AF were negative prognostic indicators. As is well known from other studies (Reef et al. 2014).

The severity and kind of valves that showed the most severe regurgitation were equally distributed in the groups in table 7. If the size of the mean LVID (d) and LA is compared between these groups some differences can be stated, however the number per groups is small and the mean cardiac measurements close to the maximum reference size of 12.5 cm for LVID(d) and 13.5 cm for LA. In all groups were horses present with a dilated left ventricle or atrium or both and the follow-up time was several years in all groups. These similarities makes it difficult to draw conclusions between the groups of follow-up and only the seven horses that are died in the field or euthanized with signs of cardiac failure stand alone in age, cardiac measurements and the presence of arrhythmia's.

The mean cardiac sizes of the 32 horses that are kept in ownership and in use after follow-up can be compared with the four horses diagnosed with *valvular regurgitations* with clinical relevant cardiac disease at the time of first examination, see table 4. They have a mean LVID(d) of 16.0 cm and an LA size of 15.1 cm and it can be concluded that these horses have a more severe cardiac chamber dilatation than the horses in follow-up. In the group of horses diagnosed with *valvular regurgitations and arrhythmias,* see table 4 and were suffering from relevant cardiac disease 12 were diagnosed with moderate or severe regurgitations and dilated cardiac chambers were evident in 11 of them. The mean LVID(d) of 14.1 cm and LA size of 14.8 cm were also much larger then the mean sizes of the follow-up horses at time of first examination from table 7. And in addition to that, these horses were suffering from arrhythmias as well. Probably the fact that many horses from the follow-up didn't had a severely dilated heart and no arrhythmias, was of great influence of the results. In the study from Gehlen, 2007b not many horses showed a deterioration of the cardiac measurements and if deterioration occurred it seemed not dependent of time of existence of the cardiac condition (Gehlen 2007b). From the 32 horses in use, 15 got reexamined at the clinic and in only one horse the cardiac measurements showed some deterioration in LA size, while in two of the horses the regurgitations even improved unexplained. Before an equine heart shows signs of failure, it seems that a diagnosis of moderate or severe regurgitation must be accompanied by several other abnormalities as severely enlarged cardiac chambers or arrhythmias and this does not happen overnight. How many years these horses can cope with their cardiac condition remains unknown and no studies have actually looked at time of onset of heart failure in horses with moderate to severe regurgitations that were not clinical relevant at the time of first consultation. It would be interesting to follow these horses in time. In the mean time, predicting the clinical course of moderate to severe regurgitations remains difficult on the long term and because of this, reexaminations are still recommended.

Acknowledgements

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