Equine Veterinary Journal

Equine Veterinary Journal ISSN 0425-1644
DOI: 10.1111/j.2042-3306.2012.00580.x

Aortic rupture and aorto-pulmonary fistulation in the Friesian horse: Characterisation of the clinical and gross *post mortem* findings in 24 cases

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Summary

Reasons for performing study: In horses, aortic sinus of Valsalva aneurysms or tears in the aortic root are well-recognised conditions in breeding stallions, often leading to sudden death. A more uncommon form of aortic rupture, located proximal to the *ligamentum arteriosum* has been reported in 3 Friesian horses.
Objectives: The purpose of this study was to phenotypically characterise aortic rupture and aorto-pulmonary fistulation in Friesian horses in terms of clinical and *post mortem* data based on 24 cases.
Methods: Friesian horses that were diagnosed with aortic rupture and aorto-pulmonary fistulation over a period of 13 years (1997–2010) at the Department of Equine Sciences of Utrecht University (n = 15) and Wolvega Equine Hospital (n = 9), were included in this study. Case history, results of clinical examination and gross *post mortem* findings were screened and analysed.
Results: Some cases were found dead without prior symptoms, but in several cases signs such as recurrent colic, peripheral oedema and sustained tachycardia were present for several weeks prior to cardiac failure. Clinical examination during hospitalisation revealed increased rectal temperature, peripheral oedema and increased jugular pulse with a bounding arterial pulse. In the majority of horses an aortic rupture of the aortic arch near the *ligamentum arteriosum*, concurrent with a circumferential cuff of perivascular haemorrhage and aorto-pulmonary fistulation, was found at *post mortem* examination.
Conclusions: Aorto-pulmonary fistulation in conjunction with aortic rupture is more common in Friesians than previously estimated. In some cases findings demonstrate a progressive pathology rather than acute cardiac failure and sudden death. An appropriate approach is necessary during *post mortem* examination of the heart in order not to overlook the diagnosis.
Potential relevance: Equine practitioners should realise that in Friesian horses presented with a history of recurrent false colic, coughing, sustained tachycardia and/or peripheral oedema, aortic rupture and aorto-pulmonary fistulation should be included in the differential diagnosis.

Keywords: horse; aorto-pulmonary fistulation; colic; jugular pulse; collagen; *ligamentum arteriosum*

Introduction

In western countries, abdominal aortic aneurysm formation and rupture is the 13th leading cause of death in man [1]. This is a multifactorial disease in which both genetic risk factors and inflammation play an important role [2]. Approximately 74% of human aortic aneurysms are in the abdominal part and approximately 23% are in the thoracic part of the aorta [3,4]. In horses, several cases of aortic root disease have been reported, which are characterised by an aneurysm of the aortic sinus of Valsalva or a tear in the aortic root. This type of aortic rupture usually occurs very close to the junction of the aorta with the heart [5,6]. Aortic root rupture is well-known in breeding stallions during coitus or shortly thereafter [7]. The rupture can result in acute haemorrhage into the pericardial sac, leading to signs of acute cardiac failure and often death within seconds. Sometimes the aorta ruptures into the right atrium, right ventricle or interventricular septum [5,8–10].

Van der Linde-Sipman *et al*. [11] reported 3 Friesian horses manifesting with aortic rupture at a more distal location, at the level of the aortic arch near the *ligamentum arteriosum*.

Since then, many similar cases in Friesian horses have been presented to Utrecht University Equine Hospital and Wolvega Equine Hospital in The Netherlands, making this specific form of aortic rupture a quite commonly encountered pathology in Friesian horses.

Thus far there is no study describing the characteristic phenotypical appearance of aortic rupture and aorto-pulmonary fistulation in the Friesian breed in a large case series, which makes this type of pathology difficult to recognise, especially in countries where the Friesian breed is less common. The purpose of this article is to describe the phenotype of this condition in terms of case history, clinical and *post mortem* data from 24 Friesian horses diagnosed with aortic rupture and/or aorto-pulmonary fistulation. This phenotypical characterisation is a first step in an attempt to unravel the pathophysiology and possibly the genetic background of this almost invariably fatal cardiac pathology in the Friesian horse breed.

Material and methods

Animals

Twenty-four Friesian horses that were diagnosed with aortic rupture or aorto-pulmonary fistulation over a period of 13 years (1997–2010) at the Department of Equine Sciences of Utrecht University (n = 15) and at Wolvega Equine Hospital (n = 9) were included in this study. Case logs were screened for case history, clinical signs at admission, haematological variables, findings at diagnostic imaging and *post mortem* examinations.

Case history

Clinical history data included age, gender, previous episodes of fever or tachycardia (pulse >50 beats/min), duration of illness (days) from the onset of overt clinical complaints, and time point of manifestation of one of the following clinical signs in the past: epistaxis, recurrent colic, coughing and (intermittent) presence of peripheral oedema (brisket, abdomen and/or prepuce).

Clinical examination at arrival

Clinical parameters included: presence of peripheral oedema, rectal temperature (°C), assessment of mucous membranes, respiratory rate (breaths/min), arterial pulse (beats/min, type), presence of carotid hammer pulse and/or jugular pulse, findings at thoracic auscultation such as pronounced vesicular breathing and shallow breathing sounds, findings at cardiac auscultation such as presence of specific murmurs, presence of cardiac arrhythmias and sustained sinus tachycardia at rest.

Haematological parameters

Haematological parameters included measurement of total white blood cell count and differentiation, packed cell volume (PCV) and thrombocytes.

Diagnostic imaging

A standard echocardiographic (Pie Medical Esaote Mylab 50[a], Philips HD 11 XE [NZE 439][b]) evaluation was performed by visualisation of the right parasternal long-axis views: 4 chamber view, the left ventricular outflow tract and the right ventricular inflow and outflow tract view during which the aortic and pulmonary artery diameter were evaluated, the area of the left ventricle in systole and diastole and fractional shortening were assessed. Right parasternal short-axis views of the left ventricle, the mitral valve and the aortic valve were obtained. Measurement of the diameter of the left ventricle in systole and diastole and evaluation of left ventricular systolic function using M-mode were performed. Finally, a left parasternal long-axis view was obtained. The dilation of the pulmonary artery, right atrium and right ventricle were based on subjective assessment.

Thoracic radiographs (Philips Super-100CP[b], Philips ZA91[c]) were used to assess the presence of pleural effusion or dilatation of the aorta.

Gross *post mortem* findings

Post mortem examination was performed according to standard procedures [12]. Attention was paid to the possible presence of the following morphological features during gross examination of the organs: lung oedema, pleural effusions, peripheral (brisket, abdomen or prepuce) oedema, aorto-pulmonary fistulation, aortic rupture near the *ligamentum arteriosum*, pulmonary artery rupture and macroscopic liver congestion (as illustrated by swollen borders and bloody appearance on cut surface).

Results

Initial case history

The primary attending practitioners reported several relevant clinical data in the study population. The reports included 14 females, 5 intact males and 4 geldings and the gender of one horse was not registered. Mean ± s.d. age at which the aortic disease was diagnosed was 4.9 ± 3.9 years (range 1–20, median 4 years). More than one-third of all cases (n = 10) showed recurrent signs such as colic, anorexia, repeated recumbency, depression, poor performance or coughing in the days or weeks prior to the fatal cardiac failure. Epistaxis was reported in 4 horses. In all cases suffering from recurrent colic, rectal examination revealed no abnormalities such as impaction or displacement of the intestine with the exception of one case, in which caecal impaction was found. Other distinctive features often reported were (intermittent) peripheral oedema (n = 8), fever (≥38.5°C; n = 5) and sustained sinus tachycardia at rest (n = 8). These latter signs were often only reported at a later stage in the disease process, 1–2 weeks before cardiac failure. Duration of overt illness was 4–9 days in 7 and ≥10 days in 9 horses. Three horses (*Cases 5*, *18* and *21*) were reported as found dead without prior manifestation of any clinical symptoms. The report of one horse (*Case 2*) was incomplete and did not contain data on all features mentioned.

Clinical examination at presentation in referral clinic

Characteristic features at presentation were increased rectal temperature (>38.5°C; n = 12), peripheral oedema (n = 11) and increased respiratory rate (n = 7; >14 breaths/min) (Table 1). The arterial pulse rate was frequently increased (>40 beats/min; n = 17) and judged to be hyperkinetic in 10 cases. Carotid hammer pulse was palpated in 3 horses and pronounced jugular pulsations were detected in the same 3 horses (Supporting item S1) was palpated in 3 cases. Pale mucous membranes were reported in 7 cases. Cardiac auscultation revealed cardiac arrhythmias (n = 3), sustained sinus tachycardia (n = 6) and presence of murmurs (n = 11), which were further characterised in 8 cases. Of these, 6 horses had a systolic murmur and 2 a diastolic murmur on the left side.

Haematology

Haematological parameters were recorded in 13 horses. White blood cell count was measured in 10 horses of which 2 showed an increased count (15.3×10^9 cells/l [reference range 5.5–12.1×10^9 cells/l] and 11.9×10^9 cells/l [5–10]). The PCV was frequently decreased (11/13; mean ± s.d. 0.25 ± 0.046 l/l, median 0.27 l/l). Thrombocytes were within reference limits for all horses.

Echocardiographic and radiographic examination

Echocardiography was performed in 16 cases and revealed a dilated pulmonary artery in 5. Three horses had a wider diameter of the pulmonary artery compared with the aortic diameter. In 6 cases a dilated right atrium was detected and 5 horses in this group also showed a dilated right ventricle. Presence of a pleural effusion was reported in 8 horses and in 3 cases a pericardial effusion was detected. In the 11 horses with murmurs only 3 also showed valvular insufficiencies. All 3 horses had tricuspid regurgitation and 2 also had mitral valve regurgitation. In one other horse there were no murmurs detected although echocardiography showed both tricuspid and mitral valve regurgitation.

Radiographic examination was performed in 5 horses (3 of which also had echocardiography). Thoracic pleural effusion was seen in 4 cases and in one horse a dilated aorta was identified.

Gross *post mortem* examination

In all cases, there was a transverse aortic rupture at the level of the aortic arch, near (1–2 cm caudal) to the *ligamentum arteriosum*. A circumferential cuff of blood around the aorta, covering the aortic rupture and extending up to 40 cm in length, was present in 8 cases (Figs 1–3). A few cases (n = 4) also had a cuff of perivascular haemorrhage around the pulmonary artery. These circumferential blood cuffs were not due to obvious aneurysmal dilatations, but were formed by leakage of blood out of the ruptured site into the connective tissue surrounding the arteries. None of the horses had concurrent aneurysmal dilatation of the arteries. The majority of the horses with aortic rupture also had an aorto-pulmonary fistulation (n = 13) with transverse pulmonary artery rupture (Supporting item S2), which was located opposite the aortic rupture and approximately 8 cm above the pulmonic semilunar valves. In 5 cases the *post mortem* records described a pronounced frayed rim of the ruptured aorta (Fig 4). In contrast the ruptures of the pulmonary arteries were in some cases described as less irregular. The route of fistulation was described as a connection between aorta and pulmonary artery with multiple pockets of 0.5–7 cm in diameter expanding the lumen in many cases (n = 10).

Pleural effusion was reported in 9 horses. In 4 of these horses there was haemothorax and mild to moderate amounts of haemorrhagic fluid was also present at the nares of these horses. Pulmonary oedema was marked and diffuse in 9 cases and in 7 of these horses a cuff of perivascular haemorrhage around the aorta with aorto-pulmonary fistulation was detected. Moderate to severe peripheral oedema (located around the ventral thorax, ventral abdominal wall and preputial sheath) was found in 7 animals and in 5 of them concurrent pulmonary oedema was also described. Congestion of the liver was reported in 10 cases and confirmed histopathologically by periacinar congestion (n = 10) with necrosis (n = 2) of

TABLE 1: Overview of clinical signs at presentation

							Thoracic auscultation		Cardiac auscultation		
Horse	Oedema	Rectal Temperature (°C)	Respiratory rate (breaths/min)	Pulse rate (beats/min)	Pronounced jugular pulsation	Bounding arterial pulse	Pronounced vesicular breathing	Shallow breathing sounds	Arrhythmias	Sustained tachycardia	Murmur
1	+	38.1	40	80	–	–	+	–	–	–	3/6, Systolic, L
2	+	39.1	NA	90	NA	–	NA	NA	NA	+	Systolic
3	–	NA	NA	80	+	+	–	+	–	–	NA
4	–	37.8	NA	90	+	–	NA	NA	–	+	–
5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
6	+	NA	NA	NA	–	–	NA	NA	NA	NA	NA
7	+	NA	NA	85	+	+	–	–	–	–	NA
8	–	38.7	NA	75	+	–	–	–	–	–	Systolic + Diastolic, L
9	+	NA	NA	100	+	+	NA	NA	NA	NA	NA
10	–	NA	NA	NA	–	–	NA	NA	NA	NA	NA
11	–	NA	NA	120	–	–	–	–	+	–	Diastolic, R
12	+	38.5	40	72	–	–	+	–	–	–	–
13	–	NA	NA	NA	–	–	NA	NA	NA	NA	NA
14	–	38.1	NA	90	+	–	–	–	–	+	Systolic, L
15	+	38.1	40	88		–	–	–	–	+	+
16	–	37.9	22	72	+	–	–	–	–	+	4/6, Systolic, L
17	+	38.4	24	80	+	–	+	+	+	+	–
18	NA	NA	NA	NA	NA	–	NA	NA	NA	NA	NA
19	+	39.0	NA	70	–	–	–	–	+	+	+
20	–	39.0	NA	80	+	–	–	–	–	–	4/6, Systolic, L
21	–	NA	NA	NA	–	–	NA	NA	NA	NA	NA
22	+	38.8	24	100	+	–	–	–	–	–	Systolic, R
23	+	38.8	12	120	–	–	+	–	–	–	4/6, Systolic + 2/6, Diastolic, L
24	+	38.9	40	80	–	–	+	+	–	–	+

+: present; –: absent; NA: data not available.

Fig 1: A marked circumferential cuff of blood around the aorta at necropsy, covering the aortic rupture and extending up to 40 cm in length.

hepatocytes and fibrosis (n = 1). Other findings were pale mucous membranes (n = 5), dilated right ventricle (n = 5) and oedema of the intestinal mesentery (n = 1).

Discussion

This demonstrates that aortic rupture in conjunction with aorto-pulmonary fistulation at the level of the aortic arch near the *ligamentum arteriosum* is much more common in Friesians than previously estimated. Van der Linde-Sipman *et al*. [11] reported on 3 Friesian horses with a similar transverse aortic rupture proximal to the scar of the former outlet of the *ductus arteriosus* of Botalli. These horses also had a transverse rupture in the pulmonary trunk opposite the aortic rupture, forming a fistulation into the pulmonary artery and functioning as a left to right shunt. Only one other case, referred to as dissecting aortic lesions connecting with the pulmonary artery, has been described in a horse from a different breed (Dutch crossbred) [11].

A feature already described by van der Linde-Sipman *et al*. [11] is the presence of haemorrhage, mainly found around the aorta, but also around the pulmonary trunk. These haemorrhages were previously regarded as dissecting aneurysms. However, it has now become clear that these were circumferential cuffs of perivascular haemorrhage formed by leakage of blood out of the ruptured site into the connective tissue surrounding

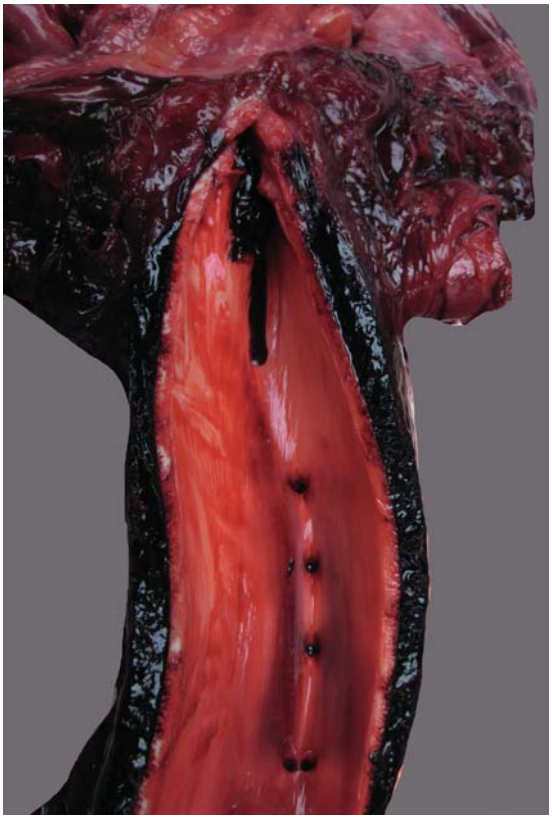

Fig 3: Longitudinal section of a marked cuff of perivascular haemorrhage around the aorta.

the arteries. This observation has consequences for the possible aethiopathogenesis and also for the nomenclature of this pathology.

Hepatic fibrosis found in one of the horses, which was considered to be a sign of chronic heart failure, indicates that aortic rupture and aorto-pulmonary fistulation in Friesian horses can manifest not only as an acute event, but also as less acute pathology, eventually culminating in acute fatal cardiac failure over the course of a few days to several weeks. It appears that some Friesian horses developed an acute aortic tear with haemothorax and subsequent death within minutes, whereas others formed an aortic tear and/or aorto-pulmonary fistulation with a cuff of

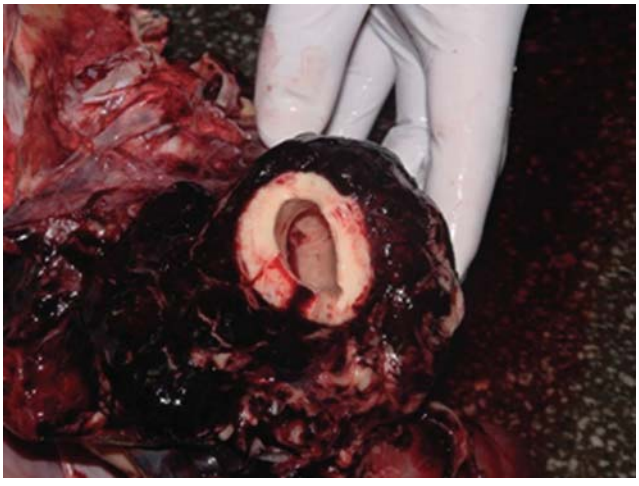

Fig 2: Cross-section of a marked cuff of perivascular haemorrhage around the aorta.

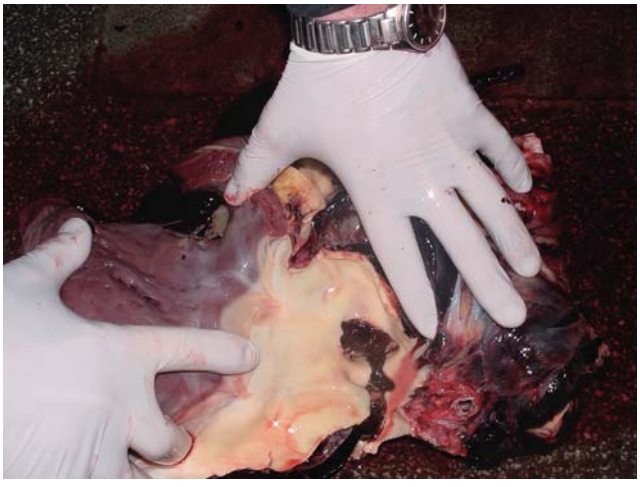

Fig 4: Aortic rupture. Note the frayed rim at the site of rupture.

perivascular haemorrhage around the aorta and/or the pulmonary artery allowing for stabilisation for several weeks in some cases. Finally, there was a group of horses that formed a quite stable aorto-pulmonary fistulation that led to right-sided heart failure, after weeks to months. In these nonacute cases, complaints such as recurrent colic, epistaxis, coughing and intermittent manifestation of peripheral oedema in the weeks prior to the final stage of overt cardiac failure were reported. Experience with these patients in the 2 equine hospitals has demonstrated that unless overt cardiac failure or haemothorax are present, some of these horses can be kept in a stable condition for several weeks. They may have intermittent peripheral oedema, but there is continuous presence of tachycardia (pulse >50 beats/min) at rest and sometimes a bounding arterial pulse. The finding of chronic liver congestion in several of these horses supports a chronic course of the disease. This slow progression makes early recognition of these patients very important and potentially offers possibilities for treatments, such as application of intravascular occlusion devices [13].

Our study demonstrates that accurate *ante mortem* diagnosis of this condition is quite challenging at present. Case history and specific clinical signs may give helpful indications. Equine clinicians should realise that aortic rupture and aorto-pulmonary fistulation should be included in the differential diagnosis when confronted with a Friesian horse that presents with a case history of recurrent nongastrointestinal related colic and/or coughing, exercise intolerance, fever, epistaxis, sustained tachycardia and possibly a bounding arterial pulse. However, these signs are not conclusive and it is clear that there is a need to develop additional techniques to diagnose this condition at an earlier stage. It should also be recognised that this aortic disease also requires a specific approach to the *post mortem* examination, especially with respect to the cardiac incisions. These should be made in such a manner that the diagnosis cannot be missed (Supporting item S3). It is therefore advised to modify the standard heart opening procedure slightly [12]: after *in situ* examination and opening of the pericardial sac, the thoracic aorta at the diaphragm should be dissected. The heart, thoracic aorta, some lung tissue that is left attached and the undamaged pulmonary artery are removed from the thoracic cavity. The left ventricle (up to the aortic valves) and atrium are opened by cutting from the apex following the caudal border of the left ventricle. Then the right ventricle and atrium are opened with a V-shaped incision with the apex of the heart forming the tip of the V. The *truncus pulmonalis* is then cut open and, when present, the edges of a pulmonary rupture can be observed. Next the dorsal side of the aorta is incised from the thoracic side towards the heart base. By cutting through the cuff of blood surrounding the aorta and transecting the aortic tear, the scar of the *ligamentum arteriosum* will be transected. In this area a small probe is needed to visualise the aorto-pulmonary fistula, if present.

There are several explanations possible for the typical localisation and presentation of aortic rupture and aorto-pulmonary fistulation in the Friesian breed. Van der Linde-Sipman *et al*. [11] proposed that the tension of the *ligamentum arteriosum* on the previously damaged walls of the aorta and pulmonary trunk might facilitate rupture. In the affected area the fibrous tissue of the *ligamentum arteriosum* connects the aorta and pulmonary trunk and this merging of different tissues may constitute a weak area in the vessel wall. Van der Linde-Sipman *et al*. [11] also described the histological features, which consisted of media necrosis and intimal thickening and/or medial fibrosis in many *vasa vasorum* in the media and adventitia of aorta and pulmonary trunk [11]. Histopathological examination of samples of the cases presented will be performed in more depth to further unravel the aetiopathogenesis as proposed by van der Linde-Sipman *et al*. [11]. Holmes *et al*. [14] proposed that the rupture of the pulmonary trunk was due to pressure necrosis induced by the haematomas around the aorta.

In man, the precise mechanism of spontaneous nonsyndromal aortic rupture without prior formation of an aneurysm is also not clear. The major pathological changes in these cases are atherosclerotic plaques together with longstanding hypertension [15]. Atherosclerotic disease is not recognised in horses, although Teeter *et al*. [16] have demonstrated the frequent presence of arterial calcifications (arteriosclerosis) in the pulmonary artery of racehorses. However, no calcifications were detected in this study.

Many human cardiac outflow tract defects appear to have an embryonic pathogenesis involving the neural crest cell lineage [17] or vascular smooth muscle cell defects [18]. Similarly, an embryological defect originating from the fusion of the dorsal aorta and the developing heart could be a possible reason for the rupture seen in the Friesian breed. Finally, besides embryological developmental aortic malformations, there are also other syndromes that could result in cardiac disease and in particular in aortic rupture. For example, Marfan syndrome is an elastin connective tissue disorder caused by fibrillin-1 gene mutation; Ehlers-Danlos is known as a collagen connective tissue defect; and Loeys-Dietz syndrome is known to be caused by heterozygous mutations in the genes encoding for *type I* or *II* transforming growth factor-beta (TGF-beta) receptor [19].

Van der Linde-Sipman *et al*. [11] suggested that a genetic susceptibility is likely, as the aortic and pulmonary trunk ruptures occurred in 3 Friesian horses that were descendants from the same sire. Van Vliet and Back [20] demonstrated that 75% of horses admitted to the Utrecht Teaching Hospital with 'aortic rupture' were of the Friesian breed, whereas Friesians comprise only 7% of the general hospital population. The Friesian breed has low levels of variation in protein and microsatellite markers, possibly due to a sharp reduction in the number of breeding stallions after World War II [21]. Whole genome scan techniques have proven to be successful in studying simple genetic diseases in the Friesian breed [22]. For complex genetic diseases it is essential to do in-depth phenotypic research, of which this study is a first step with respect to vascular pathology. The improved phenotypic description of aortic rupture in Friesians may also prove helpful to find more accurate, *ante mortem* diagnostic tools as 'early warning signs' and possibly in the development of treatment modalities that may prevent fatal rupture.

Authors' declaration of interests

No conflicts of interest have been declared.

Source of funding

This study was funded by KFPS (Dutch Royal Friesian Horses Studbook).

Acknowledgements

We would like to thank the supporting staff of the pathology Department of the Ghent and Utrecht University for their experienced technical assistance; Dr Bart Ducro of the Wageningen University for helping with the first steps in genetic research. Last but not least, we would like to thank all equine practitioners, especially Dr Pascale Drijfhout, for providing us with Friesian horses suffering from aortic rupture and Ids Hellinga, director of the Royal Friesian Horses Studbook (KFPS), for his kind cooperation and support.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Supporting Item S1: Movie demonstrating a pronounced jugular pulsation that was seen in a Friesian horse with a large shunt between the aorta and pulmonary artery.
Supporting Item S2: Movie showing *post mortem* examination of the heart of a Friesian mare. First the aorta is opened and after removal of the large blood clot localised within the transversal tear, a clear view is obtained on the fistulation chamber. The tear gives access to the aorto-pulmonary fistulation, which is represented by a 'chamber'. Through this chamber, a connection is found into, in this case, the dissected wall of the pulmonary artery.
Supporting Item S3: PDF file illustrating the main features of *post mortem* examination of a heart of a Friesian horse suspected of having aorto-pulmonary fistulation.

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