



Sudden death in racing Thoroughbred horses: An international multicentre study of *post mortem* findings

C. H. LYLE*, F. A. UZAL†, B. C. MCGORUM, H. AIDA‡, K. J. BLISSITT, J. T. CASE§, J. T. CHARLES#, I. GARDNER¶, N. HORADAGODA*, K. KUSANO§§, K. LAM™, J. D. PACK†††, T. D. PARKIN†††, R. F. SLOCOMBE#, B. D. STEWART™ and L. A. BODEN†††

Royal (Dick) School of Veterinary Studies, University of Edinburgh, Easter Bush Veterinary Centre, UK; †California Animal Health and Food Safety Laboratory System, University of California Davis, USA; ‡Equine Research Institute, §§Racehorse Hospital, Miho Training Centre, Japan; §National Library of Medicine, National Institutes of Health, United States Department of Health and Human Services; #Veterinary Clinical Centre, University of Melbourne, Australia; ¶Department of Medicine and Epidemiology, School of Veterinary Medicine, University of California, USA; *University Veterinary Teaching Hospital Camden, University of Sydney, Australia; ††Department of Veterinary Regulation and International Liaison, Hong Kong Jockey Club, Sha Tin Racecourse, Hong Kong; †††Pennsylvania National Racetrack and Pennsylvania Animal Diagnostic Laboratory, USA; and †††College of Medical, Veterinary and Life Sciences, University of Glasgow, UK.

Keywords: horse; sudden death; *post mortem*; Thoroughbred; exercise

Summary

Reasons for performing study: To improve the understanding of exercise related sudden death in Thoroughbred racehorses.

Objectives: To describe the *post mortem* findings in cases of sudden death associated with exercise in 268 Thoroughbred racehorses.

Methods: Gross and histological *post mortem* findings of 268 cases of sudden death were collated and reviewed. Cases originated from 6 racing jurisdictions around the world. Sudden death was defined as acute collapse and death in a closely observed and previously apparently healthy Thoroughbred racehorse, during, or within one hour after, exercise. Cause of death as determined by the attending pathologist was categorised as definitive, presumptive or unexplained and compared between the different populations. Cardiopulmonary lesions recorded at *post mortem* examination were compared between different populations.

Results: Pathologists recorded a definitive cause of death in 53% (143/268) of cases. Major definitive causes of sudden death included cardiac failure, apparent pulmonary failure, pulmonary haemorrhage, haemorrhage associated with pelvic fractures or with idiopathic blood vessel rupture, and spinal cord injury. A presumptive cause of death was made in 25% (67/268) of cases and death remained unexplained in 22% (58/268) of cases. There were several statistically significant inter-population differences in the cause of death and in reporting of cardiopulmonary lesions.

Conclusions: Sudden death can be attributed to a variety of causes. Causes of sudden death and the lesions found in cases of exercise-related sudden death are similar in different racing jurisdictions. However, the lesions are often not specific for the cause of death and determination of the cause of death is therefore affected by interpretation by the individual pathologist.

Introduction

Sudden death has been defined as acute death in a closely observed and previously apparently healthy animal (Lucke 1987). Sudden death associated with exercise in the apparently healthy Thoroughbred racehorse appears to be a rare occurrence; however, the risk of such events has only been quantified in racehorses in Victoria, Australia. The risk of sudden death in that population was 0.08 per 1000 starts in flat races and 0.29 per 1000 starts in jump races, and the proportion of racing fatalities classified as sudden death (proportional mortality rate of sudden death) was 19% in flat races and 3.5% in jump races (Boden *et al.* 2006). In other Thoroughbred populations where proportional mortality rates have been recorded, similar proportions of racing fatalities were attributed to sudden death: 12% (256/1981) in the UK (2000-09) (data supplied by the British Horseracing Authority, reproduced with permission) and 9% (58/659) in California, USA (Johnson *et al.* 1994a).

Several studies have reported *post mortem* findings in cases of sudden and unexpected death in mixed equine populations (Platt 1982; Brown *et al.* 1988) and in exercising Thoroughbreds (Gelberg *et al.* 1985; Gunson *et al.* 1988; Johnson *et al.* 1994b; Kiryu *et al.* 1999; Boden *et al.* 2005). Unfortunately, these studies had small numbers of cases, variable histopathological sampling methods and drew different conclusions, attributing sudden death to cardiac arrhythmias (Kiryu *et al.* 1999), exercise-induced pulmonary haemorrhage (EIPH) (Gunson *et al.* 1988) and exercise-induced cardiovascular failure (Gelberg *et al.* 1985). Well populated *post mortem* studies of sudden death cases are problematic due to the rarity of sudden death and to the logistics and economics of transporting horses to *post mortem* examination centres and performing detailed and comprehensive gross and histological examinations. Furthermore, the absence of findings to explain death in many cases has also de-incentivised such investigations. Consequently, detailed *post mortem* examinations of

*Corresponding author email: catriona.lyle@ed.ac.uk

[Paper received for publication 14.03.10; Accepted 18.05.10]

horses suffering sudden death are rarely done outside those racing jurisdictions where it is mandatory.

Risk factors for fatal racecourse events, including catastrophic musculoskeletal injuries and sudden death, have been studied (Boden *et al.* 2007a,b), but risk factors for sudden death alone are not reported, partly because of the rarity of sudden death and the difficulty in clarifying case definition without *post mortem* examination. The motivation for the present study arose from a Dorothy Havemeyer Foundation-funded workshop held in Hong Kong in April 2007 (Parkin 2007), where it was recognised that there was a need for improved understanding of the cause of sudden death. The aim of this study was therefore to collate and describe data on sudden death cases from several countries where comprehensive and detailed *post mortem* examination was done. It is hoped that improved understanding of these causes may eventually allow identification of risk and protective factors that will help minimise the risk of sudden death and improve racehorse welfare and jockey safety.

Materials and methods

Data collection

Racing jurisdictions that conduct detailed and comprehensive *post mortem* examinations on Thoroughbred racehorse casualties were identified and contacted to participate in this study. As sudden death is a relatively rare occurrence a multi-centre approach was used to obtain enough data to produce meaningful descriptive statistics. Data were collected from 6 racing jurisdictions, namely California, USA (San Bernardino, Davis and Tulare laboratories of the California Animal Health and Food Safety Laboratory System, University of California, Davis); Pennsylvania, USA (Pennsylvania Diagnostic Laboratory, Harrisburg); Victoria, Australia (Veterinary Clinical Centre, University of Melbourne); Sydney, Australia (University Veterinary Teaching Hospital Camden, University of Sydney); Hong Kong (Hong Kong Jockey Club) and Japan (Japan Racing Association). *Post mortem* examination data from these centres were searched electronically and manually for sudden death cases and data recorded using Microsoft Excel.

Case definition

Sudden death was defined as acute collapse and death in a closely observed and previously apparently healthy Thoroughbred racehorse, during, or within one hour after, exercise. Horses were excluded if a detailed *post mortem* report was unavailable, if the horse was subjected to euthanasia *in extremis*, or if there was concurrent trauma that could have contributed to death.

Demographic and event description data

Age, gender and activity at the time of death (exercise or post exercise) were recorded as categorical variables. The proportion of all horses in each of the categories was calculated for all variables. Age was also considered as a continuous variable and as such, mean, median and range were calculated.

Cause of death

Cause of death as determined by the attending pathologist was categorised as definitive, presumptive or unexplained. Cases were

defined as definitive if the pathologist was certain that the type and/or severity of gross and/or microscopic findings were compatible with sudden death. Definitive causes of death were broadly categorised as: cardiac and/or pulmonary failure, haemorrhagic shock, central nervous system (CNS) trauma, miscellaneous causes or multiple causes (i.e. combinations of the other categories). Cases were defined as presumptive if the type and/or severity of gross and/or microscopic findings were not compatible with sudden death but the pathologist speculated on the probable cause of death. Cases were defined as unexplained if the pathologist did not associate the lesions with the sudden death. The proportion of horses in each population in each of the categories was calculated for all variables.

Cardiopulmonary post mortem lesions

Cardiopulmonary lesions were categorised as acute pulmonary congestion, acute pulmonary oedema, acute pulmonary haemorrhage, chronic pulmonary lesions, gross cardiac lesions and histological cardiac lesions. The proportion of horses in each population in each of the categories was calculated for all variables. Horses could be categorised with one or more lesions. The presence or absence of chronic pulmonary changes was recorded based on histological (and gross) findings. These changes were categorised as chronic haemorrhage (presence of haemosiderophages), inflammation, fibrosis or miscellaneous changes. Perivascular and/or peribronchial mononuclear infiltration was not recorded as inflammation as, although this was a common finding, it is commonly observed in horses subjected to euthanasia with catastrophic musculoskeletal injuries (authors' unpublished observation). Histological cardiac lesions were categorised as inflammation, cellular degeneration, necrosis, fibrosis, mixed changes or miscellaneous changes.

Data and statistical analyses

Demographic data, cause of death and cardiopulmonary *post mortem* lesions were recorded separately for each racing jurisdiction and also reported collectively for all racing jurisdictions. Confidence intervals (95%) for proportions (demographic data, cause of death and cardiopulmonary lesions) were calculated using Wald's statistic (Abramson 2004). Univariable logistic regression was used to make comparisons between jurisdictions with respect to pathologists' diagnoses and the presence of cardiopulmonary lesions. These analyses were performed using STATA 10.1 statistical software¹.

Results

A total of 268 cases of sudden death were identified: 60% (162/268) from California, USA (February 1990–August 2008); 8% (22/268) from Pennsylvania, USA (February 1997–September 2007); 13% (36/268) from Victoria, Australia (February 2001–May 2008); 11% (28/268) from Sydney, Australia (January 2003–July 2009); 4% (10/268) from Hong Kong (March 2000–February 2008); and 4% (10/268) from Japan (October 1972–January 2002). Horses from California, Pennsylvania, Hong Kong and Sydney comprised only flat-racing horses while those from Japan and Victoria included flat and jump-racing horses. Proportional mortality of sudden death was 4% in California and varied from 3.5% in jump races in Victoria to 19% in flat races in Victoria

(Boden *et al.* 2006). Proportional mortality rates in the other racing jurisdictions were not available for comparison.

Demographic data

Demographic and event data are detailed in Table 1 and were similar between the different centres. When the data for all 6 jurisdictions were pooled together the median age of cases was 4 years (range 2–11 years) and mean age 4.11 years. Most cases were male (gelded or entire) (65%, 175/268). A total of 54% (144/268) of cases died at exercise, 43% (114/268) died after exercise, while the activity of 4% (10/268) of cases at the time of death was unspecified.

Post mortem examination technique

Procedure for the gross *post mortem* examination and sampling for histopathological investigation was at the discretion of the individual pathologist (29 pathologists were involved in the study: 21 from California, 1 from Pennsylvania, 2 from Victoria, one from Sydney, 2 from Japan and 2 from Hong Kong). *Post mortem* examination technique varied from gross examination with histopathological sampling of grossly affected tissues only to gross examination with routine histopathological examination of all major organs (heart, lungs, stomach, small and large intestines, spleen, liver, kidneys and brain) as well as skeletal and spinal cord sections in selected cases.

In California and Melbourne there was a standardised protocol for cardiac tissue sampling. In California 11 cardiac sites were sampled: the right ventricular free wall with right atrial posterior wall, right coronary artery and parietal leaflet of the tricuspid valve; the right ventricular outflow tract including the pulmonic valve and the pulmonic artery; the right atrial appendage; the right atrium and anterior *vena cava* along the *sulcus terminalis* at the *crista*

terminalis to include the sinus node; the left atrial appendage; the left ventricular free wall with the left atrium attached, left coronary artery and parietal leaflet of the mitral valve; anterior papillary muscle of the left ventricle; posterior papillary muscle of the left ventricle; the interventricular septum base including the atrioventricular node or common bundle, mitral valve anterior leaflet, tricuspid valve septal leaflet and part of the interatrial septum; the interventricular septum near the apex of the left ventricle to include the terminal branches of the left coronary artery and the left ventricular outflow tract including the aortic valve and aorta (Robinson and Maxie 1993). Additional sampling was carried out in certain cases. A similar protocol was followed in Melbourne.

Description of *post mortem* examination findings was variable between pathologists with some recording only abnormal findings while others also recorded normal findings. In Melbourne there was a standardised grading system for description of the gross pulmonary lesions.

Cause of death

The causes of death as determined by the attending pathologists in each individual population are listed in Table 2. A definitive cause of death was recorded by the pathologist in 53% (143/268) of cases, a presumptive cause of death was recorded in 25% (67/268) and the death remained unexplained in 22% (58/268).

The definitive diagnoses comprised cardiac and/or pulmonary failure (56%, 80/143), haemorrhagic shock (27%, 39/143), CNS trauma (13%, 18/143), miscellaneous lesions (4%, 5/143) and combinations of these pathologies (1%, 1/143). In the 56% (80/143) of cases attributed to cardiac and/or pulmonary failure, 63% (50/80) were attributed to pulmonary haemorrhage, 20% (16/80) to cardiac lesions, 3% (2/80) to combined cardiopulmonary failure (right ventricular dilation and pulmonary haemorrhage [n = 1]) and

TABLE 1: Table showing demographic and event description data for sudden death cases in the 6 different populations

		California			Pennsylvania			Victoria					
Age (years)	Mean	3.8			5.7			4.4					
	Median	4.0			6.0			4.0					
	Range	2–10			3–10			2–11					
Gender (no., %, 95% confidence interval)	Female	62	38.3%	(30.8–45.8%)	9	40.9%	(20.4–61.5%)	6	16.7%	(4.5–28.8%)			
	Male	40	24.7%	(18.1–31.3%)	3	13.6%	(0.0–28.0%)	8	22.2%	(8.6–35.8%)			
	Neutered male	59	36.4%	(29.0–43.8%)	10	45.5%	(24.6–66.3%)	22	61.1%	(45.2–77.0%)			
	Unknown	1	0.6%	(0.0–1.8%)	0	0.0%	N/A	0	0.0%	N/A			
Activity at time of death (no., %, 95% confidence interval)	Exercise	96	59.3%	(51.7–66.8%)	5	22.7%	(5.2–40.2%)	23	63.9%	(48.2–79.6%)			
	Post exercise	66	40.7%	(33.2–48.3%)	17	77.3%	(59.8–94.8%)	13	36.1%	(20.4–51.8%)			
	Unknown	0	0.0%	N/A	0	0.0%	N/A	0	0.0%	N/A			
		Sydney			Hong Kong			Japan			Total		
Age (years)	Mean	3.3			4.8			4.6			4.1		
	Median	3.0			4.5			4.0			4.0		
	Range	2–8			3–7			3–8			2–11		
Gender (no., %, 95% confidence interval)	Female	12	42.9%	(24.5–61.2%)	0	0.0%	N/A	3	30.0%	(1.6–58.4%)	92	34.3%	(28.6–40.0%)
	Male	3	10.7%	(0.0–22.2%)	0	0.0%	N/A	7	70.0%	(41.6–98.4%)	175	65.3%	(59.6–71.0%)
	Neutered male	13	46.4%	(28.0–64.9%)	10	100.0%	N/A	0	0.0%	N/A	1	0.4%	(0.0–1.1%)
	Unknown	0	0.0%	N/A	0	0.0%	N/A	0	0.0%	N/A	0	0.0%	N/A
Activity at time of death (no., %, 95% confidence interval)	Exercise	16	57.1%	(38.8–75.5%)	4	40.0%	(9.6–70.4%)	0	0.0%	N/A	144	53.7%	(47.8–59.7%)
	Post exercise	12	42.9%	(24.5–61.2%)	6	60.0%	(29.6–90.4%)	0	0.0%	N/A	114	42.5%	(36.6–48.5%)
	Unknown	0	0.0%	N/A	0	0.0%	N/A	10	100.0%	N/A	10	3.7%	(1.5–6.0%)

N/A: Not applicable.

[Correction added after online publication 9th November 2010: Percentage values update in Row: Gender, Column: California and Victoria; Row: Activity at time of death, Column: Total]

TABLE 2: Table showing cause of death as determined by the attending pathologists in the 6 different racing jurisdictions (% , 95% confidence interval)

		California (% , 95% CI)	Pennsylvania (% , 95% CI)	Victoria (% , 95% CI)
Cardiac and/or pulmonary failure	Cardiac failure	15 (9.3%, 4.8–13.7%)	0	1 (2.8%, 0.0–8.1%)
	Cardiopulmonary failure	0	0	1 (2.8%, 0.0–8.1%)
	Pulmonary failure	0	0	10 (27.8%, 13.1–42.4%)
	Pulmonary haemorrhage	21 (13.0%, 7.8–18.1%)	16 (72.7%, 54.1–91.3%)	11 (30.6%, 15.5–45.6%)
	Pulmonary thrombosis	1 (0.6%, 0.0–1.8%)	0	0
CNS trauma	CNS haemorrhage	2 (1.2%, 0.0–2.9%)	0	1 (2.8%, 0.0–8.1%)
	Cervical vertebral fracture	7 (4.3%, 1.2–7.5%)	0	4 (11.1%, 0.8–21.4%)
	Skull fracture	1 (0.6%, 0.0–1.8%)	0	0
	Skull and cervical vertebral fracture	1 (0.6%, 0.0–1.8%)	0	0
	Vertebral instability	1 (0.6%, 0.0–1.8%)	0	0
Haemorrhagic shock	Disseminated haemorrhage	4 (2.5%, 0.1–4.9%)	0	1 (2.8%, 0.0–8.1%)
	Idiopathic extra-pulmonary vascular rupture	15 (9.3%) (4.8–13.7%)	2 (9.1%) (0.0–21.1%)	2 (5.6%) (0.0–13.0%)
	Pelvic fracture	7 (4.3%, 1.2–7.5%)	0	1 (2.8%, 0.0–8.1%)
	Pulmonary vessel rupture	0	0	0
Miscellaneous	Miscellaneous	3 (1.9%, 0.0–3.9%)	0	2 (5.6%, 0.0–13.0%)
Multiple	Pulmonary failure and CNS trauma	0	0	1 (2.8%, 0.0–8.1%)
Presumptive diagnosis	Presumptive cardiac failure	33 (20.4%, 14.2–26.6%)	0	0
	Presumptive cardiopulmonary failure	2 (1.2%, 0.0–2.9%)	0	0
Unexplained diagnosis	Unexplained death	49 (30.2%, 23.2–37.3%)	4 (18.2%, 2.1–34.3%)	1 (2.8%, 0.0–8.1%)
	Total	162 (100%)	22 (100%)	36 (100%)

		Sydney (% , 95% CI)	Hong Kong (% , 95% CI)	Japan (% , 95% CI)	Total (% , 95% CI)
Cardiac and/or pulmonary failure	Cardiac failure	0	0	0	16 (6.0%, 3.1–8.8%)
	Cardiopulmonary failure	0	0	1 (10.0%, 0.0–28.6%)	2 (0.7%, 0.0–1.8%)
	Pulmonary failure	0	0	1 (10.0%, 0.0–28.6%)	11 (4.1%, 1.7–6.5%)
	Pulmonary haemorrhage	0	2 (20.0%, 0.0–44.8%)	0	50 (18.7%, 14.0–23.3%)
	Pulmonary thrombosis	0	0	0	1 (0.4%, 0.0–1.1%)
CNS trauma	CNS haemorrhage	0	0	0	3 (1.1%, 0.0–2.4%)
	Cervical vertebral fracture	0	0	0	11 (4.1%, 1.7–6.5%)
	Skull fracture	1 (3.6%, 0.0–10.4%)	0	0	2 (0.7%, 0.0–1.8%)
	Skull and cervical vertebral fracture	0	0	0	1 (0.4%, 0.0–1.1%)
	Vertebral instability	0	0	0	1 (0.4%, 0.0–1.1%)
Haemorrhagic shock	Disseminated haemorrhage	0	0	0	5 (1.9%, 0.2–3.5%)
	Idiopathic extra-pulmonary vascular rupture	2 (7.1%) (0.0–16.7%)	1 (10.0%) (0.0–28.6%)	2 (20.0%) (0.0–44.8%)	24 (9.0%) (5.5–12.4%)
	Pelvic fracture	0	0	1 (10.0%, 0.0–28.6%)	9 (3.4%, 1.2–5.5%)
	Pulmonary vessel rupture	0	0	1 (10.0%, 0.0–28.6%)	1 (0.4%, 0.0–1.1%)
Miscellaneous	Miscellaneous	0	0	0	5 (1.9%, 0.2–3.5%)
Multiple	Pulmonary failure and CNS trauma	0	0	0	1 (0.4%, 0.0–1.1%)
Presumptive diagnosis	Presumptive cardiac failure	0	3 (30.0%, 1.6–58.4%)	4 (40.0%, 9.6–70.4%)	40 (14.9%, 10.7–19.2%)
	Presumptive cardiopulmonary failure	25 (89.3%, 77.8–100.0%)	0	0	27 (10.1%, (6.5–13.7%)
Unexplained diagnosis	Unexplained death	0	4 (40.0%, 9.6–70.4%)	0	58 (21.6%, 16.7–26.6%)
	Total	28 (100%)	10 (100%)	10 (100%)	268 (100.0%)

CNS = central nervous system.

myocarditis and pulmonary oedema, congestion and haemorrhage [$n = 1$]), 14% (11/80) to pulmonary failure (combined acute pulmonary oedema, congestion and haemorrhage) and 1% (1/80) to pulmonary thrombosis.

In the 27% (39/143) of cases attributed to haemorrhagic shock, 62% (24/39) were attributed to idiopathic extra-pulmonary blood vessel rupture, 23% (9/39) to haemorrhage associated with pelvic fracture, 13% (5/39) to disseminated haemorrhage and 3% (1/39) to pulmonary vessel rupture. Details of the site of idiopathic extra-pulmonary blood vessel rupture are given in Table 3. The majority of cases of idiopathic blood vessel rupture occurred within the abdomen (71%, 17/24). In approximately half of the cases (47%, 8/17) the site of rupture could not be determined. In the remaining 53% (9/17) of cases, rupture was identified in the cranial mesenteric vessels (29%, 5/17), posterior *vena cava* (6%, 1/17), external iliac artery (6%, 1/17), vaginal artery (6%, 1/17) or internal spermatic

TABLE 3: Table showing sites of idiopathic extra-pulmonary vascular rupture for all 6 racing jurisdictions combined

	Vessel	No. of cases
Haemabdomen	External iliac artery	1
	Internal spermatic artery	1
	Mesenteric vessels	5
	Posterior <i>vena cava</i>	1
	Vaginal artery	1
	Unidentified	8
Retroperitoneal haemorrhage	Unidentified	1
Haemothorax	Aorta	2
	Unidentified	4
Total		24

TABLE 4: Univariable logistic regression demonstrating associations between racing jurisdiction and pathologists diagnoses or observation of cardiopulmonary lesions. Gross and histopathological cardiac lesions are not shown as these variables were not statistically significant ($P > 0.05$)

Racing jurisdiction	Cause of death							
	Presumptive diagnosis ($P < 0.0001$)				Diagnosis of pulmonary haemorrhage ($P < 0.0001$)			
	OR (95% CI)		P value		OR (95% CI)		P value	
California	REF				REF			
Pennsylvania	0.21	(0.10–0.78)	0.01		17.90	(6.30–50.87)	<0.001	
Victoria	0.03	(0.004–0.20)	<0.001		2.95	(1.27–6.87)	0.01	
Sydney	7.74	(2.25–26.64)	0.001		*		*	
Hong Kong	2.17	(0.54–8.67)	0.28		1.68	(0.33–8.45)	0.53	
Japan	0.62	(0.17–2.28)	0.47		*		*	

Racing jurisdiction	Cardiopulmonary lesions											
	Acute pulmonary congestion ($P = 0.0001$)		Acute pulmonary oedema ($P < 0.0001$)		Acute pulmonary haemorrhage ($P < 0.0001$)		Chronic pulmonary lesions ($P < 0.0001$)					
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value				
California	REF		REF		REF		REF					
Pennsylvania	1.03	(0.38–2.79)	0.96	0.68	(0.27–1.70)	0.41	6.53	(1.48–28.90)	0.01	0.66	(0.21–2.05)	0.47
Victoria	13.46	(1.79–101.20)	0.01	8.03	(1.85–34.73)	0.01	22.86	(3.05–171.02)	0.002	4.64	(2.17–9.90)	<0.001
Sydney	3.20	(0.92–11.14)	0.07	12.76	(1.69–96.50)	0.01	3.00	(1.09–8.31)	0.03	0.23	(0.05–0.99)	0.05
Hong Kong	0.16	(0.04–0.67)	0.01	0.47	(0.13–1.70)	0.25	*		*	1.26	(0.31–5.12)	0.74
Japan	0.90	(0.22–3.62)	0.88	1.10	(0.27–4.43)	0.89	0.16	(0.03–0.79)	0.03	*		*

Note *indicates that the variable was dropped from the analysis as it predicts failure perfectly. P values in bold were based on likelihood ratio tests.

artery (6%, 1/17). In 2 of the cases of mesenteric vein rupture, acute focal necrosis of the vein wall was identified and in another case a mesenteric tear had resulted in rupture of the mesenteric vessels. The aetiology of the rupture could not be identified in the other cases. Six cases of idiopathic extra-pulmonary thoracic blood vessel rupture occurred; 2 of these cases were due to aortic rupture but the site of rupture could not be determined in the remaining cases. The 5 cases of disseminated haemorrhage comprised widespread idiopathic haemorrhage in the musculature and subcutaneous tissues as well as in the abdomen and/or thorax. The aetiology and sources of this haemorrhage could not be established in any of these cases but the extent of haemorrhage was thought to be severe enough to have led to death. In 3 of these cases that occurred in California, toxicological testing was carried out for anticoagulant rodenticides but this was negative in all these cases.

In the 13% (18/143) of deaths attributed to CNS trauma, 60% (11/18) of cases had spinal cord trauma associated with cervical vertebral fracture, 17% (3/18) had CNS haemorrhage, 11% (2/18) had brain trauma associated with skull fracture, 6% (1/18) had CNS injury associated with both skull and cervical vertebral fractures and 6% (1/18) of cases had spinal cord trauma associated with cervical vertebral instability.

There were several statistically significant interpopulation differences in the cause of death (Table 4). The pathologist in Sydney was more likely to make a presumptive diagnosis than those in California ($P < 0.05$). In contrast, the pathologists in Pennsylvania and Victoria were less likely to make a presumptive diagnosis but more likely to make a diagnosis of pulmonary haemorrhage than those in California ($P < 0.05$). There was no difference between the other racing jurisdictions and California with respect to these diagnoses ($P > 0.05$).

The proportion of deaths attributable to cervical vertebral fracture was higher in Victoria (11%, 4/36) than elsewhere:

California 4% (7/162), Pennsylvania 0% (0/22), Sydney 0% (0/28), Hong Kong 0% (0/10) and Japan 0% (0/10), but this was not statistically significant.

Cardiopulmonary lesions identified at post mortem examination (Table 5)

Table 5 details whether the following cardiopulmonary lesions were recorded: acute pulmonary congestion, acute pulmonary oedema, acute pulmonary haemorrhage, chronic pulmonary lesions, gross cardiac lesions and histological cardiac lesions.

Table 4 details associations between racing jurisdiction and pathologists observations of cardiopulmonary lesions. In summary, compared to California, pathologists in Australian racing jurisdictions were more likely to record acute and chronic pulmonary lesions ($P < 0.05$), pathologists in Pennsylvania were more likely to record pulmonary haemorrhage ($P < 0.05$), pathologists in Hong Kong were less likely to report acute pulmonary congestion ($P < 0.05$), and pathologists in Japan were less likely to record acute pulmonary haemorrhage ($P < 0.05$).

Chronic pulmonary lesions identified were evidence of previous pulmonary haemorrhage (characterised by the presence of hemosiderophages), chronic inflammation, fibrosis and miscellaneous changes, e.g. parenchymal or vascular mineralisation. The numbers of cases in which these findings were identified are detailed in Table 6.

Gross cardiac lesions were only reported in 3 populations, namely California (7%, 11/162), Victoria (6%, 2/36) and Japan (1%, 1/10). These lesions consisted of dilation ($n = 3$), valvular changes ($n = 3$), right atrial hypertrophy and right ventricular dilation ($n = 1$), left ventricular hypertrophy and aortic stenosis ($n = 1$), subendocardial fibroelastosis and trabecular hypertrophy ($n = 1$) and other miscellaneous changes ($n = 4$).

TABLE 5: Table showing frequency of cardiopulmonary lesions recorded at *post mortem* examination by pathologists in the 6 different racing jurisdictions (% , 95% confidence interval)

	California (%, 95% CI)	Pennsylvania (%, 95% CI)	Victoria (%, 95% CI)	Sydney (%, 95% CI)	Hong Kong (%, 95% CI)	Japan (%, 95% CI)	Total (%, 95% CI)
Acute pulmonary congestion	117/162 (72.2%, 65.3–79.1%)	16/22 (72.7%, 54.1–91.3%)	35/36 (97.2%, 91.9–100.0%)	25 /28 (89.3%, 77.8–100.0%)	3/10 (30.0% 1.6–58.4%)	7/10 (70.0%, 41.6–98.4%)	203/268 (75.7%, 70.6–80.9%)
Acute pulmonary oedema	110/162 (67.9%, 60.7–75.1%)	3/22 (13.6%, 0.0–28.0%)	34/36 (94.4%, 87.0–100.0%)	27/28 (96.4%, 89.6–100.0%)	5/10 (50.0% 19.0–81.0%)	0	179/268 (66.8%, 61.2–72.4%)
Acute pulmonary haemorrhage	98/162 (60.5%, 53.0–68.0%)	20/22 (90.9%, 78.9–100.0%)	35/36 (97.2%, 91.9–100.0%)	23/28 (82.1%, 68.0–96.3%)	10/10 (100.0%, 100.0–100.0%)	2/10 (20.0%, 0.0–44.8%)	188/268 (70.1%, 64.7–75.6%)
Chronic pulmonary lesions	41/162 (25.3%, 18.6–32.0%)	4/22 (18.2%, 2.1–34.3%)	22/36 (61.1%, 45.2–77.0%)	2/28 (7.1%, 0.0–16.7%)	3/10 (30.0%, 1.6–58.4%)	0	72/268 (26.9%, 21.6–32.2%)
Gross cardiac lesions	11 /162 (6.8%, 2.9–10.7%)	0	2/36 (5.6%, 0.0–13.0%)	0	0	1/10 (10.0%, 0.0–28.6%)	14/268 (5.2%, 2.6–7.9%)
Histological cardiac lesions	51/162 (31.5%, 24.3–38.6%)	0	11 /36 (30.6%, 15.5–45.6%)	0	2/10 (20.0%, 0.0–44.8%)	2 /10 (20.0%, 0.0–44.8%)	66/268 (24.6%, 19.5–29.8%)

TABLE 6: Table showing number of cases from all 6 racing jurisdictions combined with different categories of chronic pulmonary lesions and histological cardiac lesions

	Type of lesion	No. of cases
Chronic pulmonary lesions	Haemosiderophages*	58
	Chronic inflammation	14
	Fibrosis	11
	Miscellaneous	7
Histological cardiac lesions	Inflammation	27
	Cellular degeneration	4
	Necrosis	3
	Fibrosis	4
	Mixed changes	18
	Miscellaneous	3

*Some cases with haemosiderophages also had chronic inflammation, fibrosis or other miscellaneous changes so some cases are classified twice.

Histological cardiac lesions identified included endocardial and/or myocardial inflammation, cellular degeneration (myocardial degeneration consisting of hypercontraction bands or hyper eosinophilic cytoplasm with pyknotic nuclei and valvular endocardiosis), necrosis, fibrosis, mixed changes and miscellaneous changes (see Table 6). These were reported in 4 populations, namely California (32%, 51/162), Victoria (31%, 11/36), Hong Kong (20%, 2/10) and Japan (20%, 2/10). The differences in reporting gross and histological cardiac lesions were not statistically significant.

Discussion

This is the largest and most comprehensive study describing *post mortem* findings of exercise-related sudden death in Thoroughbred racehorses. The large variation in the total numbers of cases from the 6 centres probably reflects differences in numbers of racehorses in training in the different areas, the time period over which the cases were collected and the legal requirements for *post mortem* investigation in different jurisdictions rather than significant differences in incidence of sudden death between the centres. The median age of 4 years and majority of male cases probably reflects the demographics of the racing populations in the 6 centres.

Cause of death

Aortic rupture, which is anecdotally thought to be a common cause of exercise-related sudden death in horses, occurred in only 1% (2/268) of cases.

In the 54% (67/125) of cases in which the pathologists made a presumptive diagnosis, they suggested that death was probably due to cardiac/cardiopulmonary failure. In this respect, the absence of significant gross and histological cardiac lesions did not preclude a diagnosis of fatal cardiac arrhythmia or other acute myocardial disease as light microscopic changes of cell death may not occur in the myocardium until up to 12 h after total ischaemia (Schoen 1999) and because arrhythmogenesis may reflect a functional rather than a structural cell abnormality. Primary conduction abnormalities including accessory conduction pathways and ion channelopathies, which may cause sudden death in human athletes (Ng and Maginot 2007), characteristically have negative *post mortem* examinations. In such cases the cause of death is determined from *ante mortem* detection of a conduction abnormality, electrocardiographic screening of relatives and/or genetic screening of relatives and/or the affected individual (a so called 'molecular autopsy') (Priori *et al.* 2001; Tester and Ackerman 2006). Primary cardiac channelopathies are as yet not described in the horse, and may be more difficult to detect than in man given the comparatively limited information obtained from equine electrocardiograms.

There were significant differences between populations in the proportion of presumptive diagnoses and the proportion of deaths attributable to pulmonary haemorrhage. These differences probably reflect differences in interpretation of cardiopulmonary lesions by the individual pathologists and are discussed later. The higher (but statistically insignificant) proportion of cervical vertebral fractures in Victoria probably reflects the participation of this population in jump and flat-racing. Pathologists commented that it was difficult to determine if severe CNS lesions were the primary cause of death or if these were secondary to falls due to collapse due to cardiopulmonary disease. In some cases from California, race videos were assessed by pathologists in an attempt to aid differentiation of primary and secondary CNS pathology, but this was found to be unrewarding (authors' unpublished observation).

Cardiopulmonary lesions

There were significant interpopulation differences in reporting of pulmonary lesions. This probably reflected differences in *post mortem* reporting protocols rather than in prevalence. For example, these lesions were reported more frequently from Victoria, where *post mortem* protocol for these cases includes grading such lesions. As pulmonary congestion and oedema are common findings in

horses subjected to euthanasia with barbiturates and may occur in the agonal stages of diseases that terminate in cardiac failure (Smith 2007), these lesions are not considered specific for any particular cause of death. Pathologists may therefore not have described these lesions because of their lack of specificity in relation to the cause of death, if protocol did not specifically require reporting of the lesions. Equally, there may have been differences in the severity and distribution of these lesions but it was not possible to report these accurately due to the variability in tissue sampling, recording and interpretation of these lesions.

Pulmonary haemorrhage was described commonly in all centres other than Japan. EIPH is a common condition in Thoroughbred racehorses with estimates of prevalence up to 80% (Sweeney *et al.* 1990). Severe EIPH has been described as a cause of exercise-related sudden death in one study (Gunson *et al.* 1988). However, it is unclear whether the severe acute pulmonary haemorrhage seen in cases of sudden death is a fulminant manifestation of EIPH and thus whether it has the same aetiology as EIPH. Interestingly, hemosiderophages (indicators of chronic haemorrhage) were not frequently recorded in horses with acute pulmonary haemorrhage, suggesting that these cases were not fulminant cases of chronic/recurrent EIPH.

The high frequency of pulmonary oedema, congestion and haemorrhage in this study is similar to findings in previous studies (Gelberg *et al.* 1985; Gunson *et al.* 1988; Johnson *et al.* 1994a,b; Boden *et al.* 2005), but pathologists varied in their interpretation as to how these lesions were related to death. In total, pulmonary haemorrhage was described in 70% (188/268) of cases but death was only attributed to this lesion in 18% (50/268) of cases. Contribution of this lesion to death was determined by severity of the lesion and by the significance attached to this lesion by individual pathologists. In some centres a much higher proportion of cases with pulmonary haemorrhage were considered to have died as a result of this lesion. This did not appear to be due to increased severity of the pulmonary haemorrhage in these populations but rather due to increased significance being attached to the finding of pulmonary haemorrhage. For example, in Pennsylvania, 91% (20/22) of cases had pulmonary haemorrhage and death was attributed to this lesion in 73% (16/22) of cases, while in California, pulmonary haemorrhage was described in 61% (98/162) of cases but death was attributed to this lesion in only 13% (21/162) of cases. This variability in interpretation has been illustrated in previous studies (Gelberg *et al.* 1985; Gunson *et al.* 1988). Unfortunately severity of the pulmonary haemorrhage could not be compared objectively between cases due to variability in tissue sampling and description. The significance of acute pulmonary oedema, congestion and haemorrhage is further complicated by the fact that many pathologists suggested that the acute pulmonary changes (oedema, congestion and haemorrhage) could be the result of cardiac failure rather than pulmonary failure. Pulmonary oedema and congestion are well described as a consequence of left-sided heart failure, and it is possible that this was due to a sudden increase in left atrial pressure as a result of arrhythmogenic cardiac failure. To complicate matters further, pulmonary oedema, congestion and haemorrhage are frequently observed in racehorses subjected to euthanasia because of catastrophic limb fracture (authors' unpublished observation) illustrating that these lesions may not necessarily represent the cause of death in sudden death cases. As the prevalence of these acute pulmonary lesions in horses that died or were subjected to euthanasia for other reasons has not been determined, it is difficult

to determine the contribution of physiological variation, agonal changes, primary pulmonary pathology and secondary pulmonary pathology (i.e. secondary to cardiac disease) to these findings. There is a need for a consensus on description and interpretation of these lesions to facilitate comparison of data from different centres.

Gross cardiac abnormalities were only described in 5% (14/268) of cases and histological cardiac lesions were only described in 25% (66/268) (see Table 3). This lack of observed structural abnormalities contrasts with sudden death in young human athletes where structural heart diseases (hypertrophic cardiomyopathy, anomalous coronary arteries and arrhythmogenic right ventricular cardiomyopathy) account for the majority of cases (Maron *et al.* 1996; Corrado *et al.* 2001).

Higher (but statistically insignificant) proportions of gross and histological cardiac lesions were described in California and Victoria, probably reflecting the more extensive cardiac dissection and sampling protocol used in these centres. The thorough protocol for cardiac dissection in these centres (Robinson and Maxie 1993) suggests that the absence of cardiac lesions in the majority of the cases is real, rather than a reflection of inadequate sampling.

Death was definitively attributed to cardiac failure in only 16/268 (6%) cases (see Table 2). In general, death was not attributed to histological cardiac lesions unless the lesions were severe and/or extensive and/or the lesions were located in the conduction tissue, although nonconduction tissue is also capable of action potential generation and hence arrhythmogenesis (Rubart and Zipes 2008). Similar gross and histological cardiac lesions have been recognised in Thoroughbreds subjected to euthanasia following catastrophic fracture on the track (authors' unpublished observation), again illustrating that cause of death may not necessarily be associated with *post mortem* cardiac lesions. The present study therefore emphasises the need for thorough systematic dissection of the heart in a control population of normal Thoroughbreds, in order to help determine the significance of such myocardial lesions in cases of sudden death and in the wider Thoroughbred population.

The variation in *post mortem* technique and description of lesions illustrates the need for a standardised protocol in cases of sudden death. In this study different techniques of pathological examination of the heart and lungs and description of cardiopulmonary lesions were not critically evaluated, so a validated *post mortem* protocol cannot be derived from the data in this study. However, to facilitate diagnosis and possible future investigation it is advisable to take samples for histopathology from both the heart and lungs even if there is no gross pathology.

Acknowledgements

The Horserace Betting Levy Board who fund C.L.'s Senior Clinical Training Scholarship at the University of Edinburgh; the contributing centres (the California Horseracing Board, the California Animal Health and Food Safety Laboratory System, University California Davis, Penn National Race Track, the Pennsylvania Animal Diagnostic Laboratory Harrisburg, Racing Victoria Ltd, the University of Melbourne, Racing New South Wales, the University of Sydney, Department of Veterinary Clinical Services Hong Kong Jockey Club and the Japan Racing Association); the contributing pathologists (Adaska, J., Anderson, M., Barr, B., Blanchard, P., Corson, B., Daft, B., Diab, S., Farman, C., Ghoddus, M., Johnson, B., Kinde, H., La Roche, D., Loretta, A., Moore, J., Mysore, J., Odani, J., Pesaven, P., Read, D., Shahriar,

M., Stleger, J., Woods, L.); the racecourse veterinarians and the Dorothy Havemeyer Foundation.

Manufacturer's address

¹StataCorp, College Station, Texas, USA.

References

- Abramson, J.H. (2004) WINPEPI (PEPI-for-Windows): Computer programs for epidemiologists. *Epidemiol. Perspect. Innov.* **1**, 6.
- Boden, L.A., Charles, J.A., Slocombe, R.F., Sandy, J.R., Finnin, P.J., Morton, J.M. and Clarke, A.F. (2005) Sudden death in racing Thoroughbreds in Victoria, Australia. *Equine vet. J.* **37**, 269-271.
- Boden, L.A., Anderson, G.A., Charles, J.A., Morgan, K.L., Morton, J.M., Parkin, T.D., Slocombe, R.F. and Clarke, A.F. (2006) Risk of fatality and causes of death of Thoroughbred horses associated with racing in Victoria, Australia: 1989-2004. *Equine vet. J.* **38**, 312-318.
- Boden, L.A., Anderson, G.A., Charles, J.A., Morgan, K.L., Morton, J.M., Parkin, T.D., Clarke, A.F. and Slocombe, R.F. (2007a) Risk factors for Thoroughbred racehorse fatality in flat starts in Victoria, Australia (1989-2004). *Equine vet. J.* **39**, 430-437.
- Boden, L.A., Anderson, G.A., Charles, J.A., Morgan, K.L., Morton, J.M., Parkin, T.D., Clarke, A.F. and Slocombe, R.F. (2007b) Risk factors for Thoroughbred racehorse fatality in jump starts in Victoria, Australia (1989-2004). *Equine vet. J.* **39**, 422-428.
- Brown, C.M., Kaneene, J.B. and Taylor, R.F. (1988) Sudden and unexpected death in horses and ponies: An analysis of 200 cases. *Equine vet. J.* **20**, 99-103.
- Corrado, D., Basso, C. and Thiene, G. (2001) Sudden cardiac death in young people with apparently normal heart. *Cardiovasc. Res.* **50**, 399-408.
- Gelberg, H.B., Zachary, J.F., Everitt, J.I., Jensen, R.C. and Smetzer, D.L. (1985) Sudden death in training and racing Thoroughbred horses. *J. Am. vet. med. Ass.* **187**, 1354-1356.
- Gunson, D.E., Sweeney, C.R. and Soma, L.R. (1988) Sudden death attributable to exercise-induced pulmonary hemorrhage in racehorses: Nine cases (1981-1983). *J. Am. vet. med. Ass.* **193**, 102-106.
- Johnson, B., Ardans, A., Stover, S.M., Daft, B., Kinde, H., Read, D.H., Barr, B.C., Moore, J., Woods, L., Anderson, M., Stolz, J. and Blanchard, P. (1994a) California racehorse *postmortem* program: A 4-year overview. *Proc. Am. Ass. equine Practns.* **40**, 167-169.
- Johnson, B.J., Stover, S.M., Daft, B.M., Kinde, H., Read, D.H., Barr, B.C., Anderson, M., Moore, J., Woods, L., Stoltz, J. and Blanchard, P. (1994b) Causes of death in racehorses over a 2 year period. *Equine vet. J.* **26**, 327-330.
- Kiryu, K., Machida, N., Kashida, Y., Yoshihara, T., Amada, A. and Yamamoto, T. (1999) Pathologic and electrocardiographic findings in sudden cardiac death in racehorses. *J. vet. med. Sci.* **61**, 921-928.
- Lucke, V.M. (1987) Sudden death. *Equine vet. J.* **19**, 85-86.
- Maron, B.J., Shirani, J., Poliac, L.C., Mathenge, R., Roberts, W.C. and Mueller, F.O. (1996) Sudden death in young competitive athletes. Clinical, demographic, and pathological profiles. *J. Am. med. Ass.* **276**, 199-204.
- Ng, B. and Maginot, K.R. (2007) Sudden cardiac death in young athletes: Trying to find the needle in the haystack. *WMJ* **106**, 335-342.
- Parkin, T.D. (2007) Epidemiology of training and racing injuries. *Equine vet. J.* **39**, 466-469.
- Platt, H. (1982) Sudden and unexpected deaths in horses: A review of 69 cases. *Br. vet. J.* **138**, 417-429.
- Priori, S.G., Napolitano, C. and Grillo, M. (2001) Concealed arrhythmogenic syndromes: The hidden substrate of idiopathic ventricular fibrillation? *Cardiovasc. Res.* **50**, 218-223.
- Robinson, W.F. and Maxie, M.G. (1993) The cardiovascular system. In: *Pathology of Domestic Animals*, 4th edn., Eds: K.V.F. Jubb, P.C. Kennedy and N. Palmer, Academic Press Inc., San Diego. pp 7-8.
- Rubart, M. and Zipes, D.P. (2008) Genesis of cardiac arrhythmias: Electrophysiological considerations. In: *Braunwald's Heart Disease*, 8th edn., Eds: P. Libby, R.O. Bonow, D.L. Mann and D.P. Zipes, Saunders Elsevier, Philadelphia. pp 746-777.
- Schoen, F.J. (1999) The heart. In: *Robbins Pathologic Basis of Disease*, 6th edn., Eds: R.S. Cotran, V. Kumar and T. Collins, W.B. Saunders, Philadelphia. p 558.
- Smith, K.C. (2007) *Post-mortem* examination. In: *Equine Respiratory Medicine and Surgery*, Eds: B.C. McGorum, P.M. Dixon, N.E. Robinson and J. Schumacher, Saunders Elsevier, Edinburgh. p 279.
- Sweeney, C.R., Soma, L.R., Maxson, A.D., Thompson, J.E., Holcombe, S.J. and Spencer, P.A. (1990) Effects of furosemide on the racing times of Thoroughbreds. *Am. J. vet. Res.* **51**, 772-778.
- Tester, D.J. and Ackerman, M.J. (2006) The role of molecular autopsy in unexplained sudden cardiac death. *Curr. Opin. Cardiol.* **21**, 166-172.

Author contributions The initiation, conception and planning for this study was by L.B., T.P., I.G., J.Ca., K.B., B.M., F.U. and C.L., with execution by C.L., F.U., J.Ca., J.Cl., R.S., N.H., H.A., K.K., B.S., K.L. and J.P., writing by C.L., B.M., F.U., L.B. and T.P. and statistics by L.B. and T.P.