Exercise-induced pulmonary haemorrhage: A progressive disease affecting performance? Exercise-induced pulmonary haemorrhage
In this edition of the *Equine Veterinary Journal*, three epidemiological investigations address the impact of exercise-induced pulmonary haemorrhage (EIPH) on Thoroughbred racehorses. In prospective studies, Sullivan et al. followed the racing career of 744 Australian Thoroughbreds after a single post-race endoscopic examination [1], while Morley et al. enrolled 1000 South African Thoroughbreds to compare the race performance of EIPH-positive and -negative horses [2]. These investigations found that EIPH, even an EIPH score of 1 [2], affects performance. In contrast, Preston and coworkers used Hong Kong Jockey Club records to examine the racing careers of 822 Thoroughbred geldings imported from New Zealand. This investigation, in which horses were examined multiple times (median 15), often by different veterinarians, found no effect of EIPH on length of racing career [3]. Despite differences in experimental design, a topic which will be vigorously debated by epidemiologists, the balance of these investigations is that EIPH affects performance. The EIPH prevalence was similar in the three locales and, although one might question the value of the single examination used by Sullivan et al. to predict racing career [1], Preston et al. confirmed that the majority of horses maintained a consistently low EIPH grade on repeated examination [3]. Hence, the EIPH score was considered in horses that had at least one serious bleed during their career. The findings in these papers raise the issues of disease progression in EIPH and of the value of EIPH score as an indicator of the presence and severity of lung lesions. A review of the pathogenesis of EIPH is pertinent to these questions.

Thoroughbred racehorses have been selectively bred for speed. Densely packed muscle mitochondria provide a very high maximal oxygen consumption (220 ml/kg bw/min), requiring a huge cardiac output (240–450 l/min or more) for lung to muscle oxygen transport. The high cardiac output is achieved by a heart beating about 4 times per second with a stroke volume 1.7 l or more. At this rapid heart rate, the cardiac cycle lasts only 0.25 s, so the ventricles must receive the 1.7 l in approximately 0.125 s, which requires a very high ventricular filling pressure that is provided by the left atrium. Pertinent to EIPH, left atrial pressure reaches 70 mmHg or more during high-speed exercise. To maintain the driving pressure for blood flow through the lung, the pulmonary arterial pressure also has to increase to 90–140 mmHg. Given that the pulmonary capillaries lie between the pulmonary artery and the left atrium, their pressure is at least 80 mmHg [see Poole and Erickson [4] for review]. In 1993, West and coworkers proposed that this pressure was causing pulmonary capillary stress failure, which they concluded was the major cause of EIPH [5]. While there is little doubt that capillary failure is the ultimate cause of bleeding, it is a transient condition and resolves when the pressure is reduced. However, the lesions that are present in the lungs of horses with EIPH suggest that much more is going on than simple reversible stress failure [6–8].

It is important to distinguish the high pulmonary arterial pressure that occurs in horses during intense exercise from that occurring in the approximately 15 per 1,000,000 people with idiopathic pulmonary hypertension [9]. Idiopathic pulmonary hypertension is due to pulmonary arterial obstruction by varying degrees of hypertrophy/hyperplasia of the media and/or intima of the pulmonary arteries. Vascular resistance is increased in the arteries, which are upstream from the capillaries, consequently left atrial and, therefore, pulmonary capillary pressure remain within almost normal limits. In exercising horses, in contrast, the increased pulmonary arterial pressure is originating to a large degree downstream from the capillaries as a consequence of the elevated left atrial pressure. As blood backs up into the lungs, venous and then capillary pressure increase, similar to left heart failure [10]. The lesions of EIPH reflect that situation. The bilateral gross lesions are characterised by varying degrees of blue-black discoloration of the pleural surface that is a consequence of haemosiderin accumulation. Haemosiderin is accompanied by fibrosis of the alveolar and interlobular septa and of the pleura, which makes the lung firm to the touch and unable to deflate fully when the lungs are excised. Vasculogenesis, probably from the bronchial circulation, also occurs within the lesions and may provide a low-resistance conduit between the systemic circulation and pulmonary capillaries within the lesion. Most importantly, there is striking remodelling of the small pulmonary veins (100–200 μm outer diameter) characterised mainly by accumulation of adventitial collagen and, in some vessels, smooth muscle hyperplasia. In the most severely affected vessels, the vascular lumen is significantly reduced [6–8]. Given that remodelled veins can be mistaken for pulmonary arteries, earlier investigations may have described similar vascular changes using terms such as ‘vascular lesions typical of hypertension’ [11] or ‘medial thickening of arterioles’ [12]. Venous remodelling can occur without haemosiderin, but the inverse rarely occurs; fibrosis never occurs without the other 2 lesions [8]. The EIPH lesion distribution (most extensive in the caudodorsal region and less common more cranially and ventrally) matches the distribution of pulmonary blood flow [13,14].

Venous remodelling typically occurs when there is elevated venous transmural pressure and/or increased shear stress on the endothelium. An example familiar to most readers occurs when saphenous veins are used to replace blocked arteries in the human heart or extremities. In order to withstand the higher pressure, the saphenous veins remodel; medial and intimal thickening occur in response to pressure and endothelial shear stress, respectively [15]. We have proposed that remodelling of small pulmonary veins of the racing horse is a response to the high flow and/or pressure to which the small veins are exposed during intense exercise [6–8]. As its wall thickens, the small vein becomes less compliant [16] and, therefore, unable to distend to accommodate the high blood flow of exercise. This downstream obstruction further raises the capillary pressure, which increases the tendency to stress failure. In this scenario, the first affected regions of lung should be those in which flow is greatest, i.e. parts of the dorsocaudal region where local blood flow can be up to 20-fold higher than in cranioventral regions [13,14]. As veins become obstructed in one region, however, flow will be diverted to adjacent regions, setting off the same scenario and gradually spreading the remodelling forwards and downwards from the initial site.

Venous remodelling is likely to begin when horses first enter training. Lesions occur in un raced Thoroughbreds in training [12], and elevated left atrial pressure does not require racing speed but occurs during speeds used in gallops. An individual horse’s degree of remodelling will be determined by the frequency and duration of the ‘high-pressure event’ (HPE) (i.e., gallops, breezes or races) and the individual horse’s vascular sensitivity to the HPE. Some low-sensitivity animals may remodel little even after many HPEs and never bleed; others with very high sensitivity may remodel with only a few HPEs and bleed copiously on their first race. The majority of horses will fall in the middle range of the normal distribution of sensitivity to HPE. These may be the animals with grade 1, a score at which they are less likely to win [2] but their duration of career is unlikely to be affected [1,3]. In the most sensitive of this middle range of horses [grade ≥2], performance will be affected by the lesions in their lungs and, as the EIPH lesions expand, earning potential will reduce or horses will race at a lower class. Although this hypothesis must remain untested until the extent of pulmonary lesions in racehorses can be quantified, the following observations are supportive: EIPH lesions occur in trained but unraced animals [12]; raced horses have stiffer small pulmonary veins than unraced horses [16]; and there is evidence that EIPH is related to the number of lifetime starts rather than age [17].

Is it reasonable to expect the EIPH score to correlate with lesion severity? Almost certainly, for the horses with grade 0 no lesions would be expected. Given that an EIPH score of 1 is associated solely with a reduced chance of winning but not of placing [2], it might be difficult to detect lesions other than capillary stress failure. It is likely that most horses with grade 2 or higher EIPH have lung lesions, microscopic if not gross. By the time a horse’s EIPH cannot be managed, they probably all have significant gross lesions occupying 30% or more of the caudal lung lobe [8]. We have noted considerable variation in the extent and severity of the lesions in horses retired because of EIPH, but an accurate history of the onset and
progression of bleeding was not available. The lesions are very complex, so that blood could be originating from regions currently undergoing remodelling or from neovascularisation in lesions as described above. With regard to the source of neovascularisation, the arterisation may be proceeding from the bronchial arteries [18] into an extensively remodelling capillary bed [19]. Given that the bronchial artery is a systemic artery, the blood entering the neovascularised lesion and its adjacent capillaries may be at higher pressure and may or may not be able to escape from within the lesion in order to become visible on endoscopy. It is not surprising to us, therefore, that given the pathology of EIPH lesions, Preston et al. found considerable variation in EIPH scores in horses with high EIPH score at least once in their careers [3].

To understand the pathogenesis and progression of the disease, it will be essential to conduct more investigations of lung pathology in horses with a variety of EIPH scores at various stages of their careers. In order to make a valid assessment of the extent and severity of lung lesions, it will be necessary to use a statistically valid but time-consuming sampling method, such as that used by Williams et al. [8]. From the clinical viewpoint, it will be vital to develop ways to determine the extent of lesions in vivo. If that were possible, then EIPH-affected horses could be evaluated before making recommendations concerning their future career. The more difficult task will be preventing the development of lung lesions, because this will require fewer or less intense HPEs, which will require altered training methods. Alternatively, it may be possible to select against horses that are very sensitive to HPEs by not breeding from animals that develop high EIPH scores.

Authors' declaration of interests

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