Distribution of venous remodeling in exercise-induced pulmonary hemorrhage of horses follows reported blood flow distribution in the equine lung

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Williams KJ, Robinson NE, DeFeijter-Rupp H, Millerick-May M, Stack A, Hauptman J, Derksen FJ. Distribution of venous remodeling in exercise-induced pulmonary hemorrhage of horses follows reported blood flow distribution in the equine lung. J Appl Physiol 114: 869–878, 2013. First published January 31, 2013; doi:10.1152/japplphysiol.01170.2012.—Exercise-induced pulmonary hemorrhage (EIPH), which has been reported in humans and a variety of domestic animals following strenuous exercise, is most often documented in racehorses. Remodeling of pulmonary veins (VR) in equine EIPH was recently described, suggesting that it contributes to the pathogenesis of the disease. The cause of VR is unknown. We tested the hypothesis that the development of VR follows pulmonary blood flow distribution, preferentially occurring in the caudodorsal lung region. Furthermore, we hypothesized that VR underpins development of the other lesions of EIPH pathology. The lungs of 10 EIPH-affected horses and 8 controls were randomly sampled for histopathology (2,520 samples) and blindly scored for presence and severity of VR, hemosiderin (H), and interstitial fibrosis (IF). Mean sample score (MSS), mean lesion score, and percent samples with lesions were determined in four dorsal and three ventral lung regions, and the frequency, spatial distribution, and severity of lesions were determined. MSS for VR and H were significantly greater dorsally than ventrally (P < 0.001) and also decreased significantly in the caudocranial direction (P < 0.001). IF decreased only in the caudocranial direction. The percent samples with lesions followed the same distribution as MSS. VR often was accompanied by H; IF never occurred without VR and H. Similarity of the distribution of EIPH lesions and the reported fractal distribution of pulmonary blood flow suggests that VR develops in regions of high blood flow. Further experiments are necessary to determine whether VR is central to the pathogenesis of EIPH.

venous remodeling; hemosiderin; pulmonary veins; exercise
the lung, so that it is most extensive and severe in the caudodorsal lung and wanes in the cranial and ventral lung. Furthermore, because we hypothesize that VR is essential for the development of other lesions of EIPH, it stands to reason that VR will occur first and be present before the full expression of EIPH pathology (44).

MATERIALS AND METHODS

Horses. Ten EIPH-affected horses (9 Thoroughbreds and 1 Standardbred) were identified by racetrack veterinarians and donated to Michigan State University for study, after retirement, because of persistent EIPH. Seven of ten horses had a history of epistaxis during racing, and eight of ten had an endoscopic EIPH grade of 3 or greater at their last examination. Because of the difficulty in acquiring EIPH-affected animals by donation, one horse was included in the study based solely on a history of previous EIPH provided by the veterinarian. Based on the examination of racing records, the median time between the last race and euthanasia was 30 days (range: 10–406 days). The horse that had not raced for 406 days remained in training, and the last reported episode of EIPH occurred 128 days before euthanasia. Control horses were selected to minimize the chance of previous EIPH and included four Thoroughbreds and one Standardbred that had never trained or raced, one Standardbred-Quarter horse cross, one Arabian-cross, and one mixed-breed riding horse. The median age of the EIPH-affected and control horses was 4.5 (range: 3–11) and 2.5 (range: 1–15) yr, respectively. Horses were euthanized with an overdose of pentobarbital sodium. The All-University Committee on Animal Use and Care at Michigan State University approved the study.

Postmortem tissue collection. Following euthanasia, the entire cardiopulmonary system was removed from the thoracic cavity. The heart and lungs were inspected and palpated, and the visceral surface of the lungs was photographed. The main-stem bronchi of the right and left lungs were cannulated, and lungs were inflation fixed with 10% neutral buffered formalin at a pressure of 30 cmH₂O and floated in a bath. After fixation, the caudal two-thirds of each lung were cut in the transverse plane into sixteen 1.5-cm thick slices, labeled 1 through 16 (cranial to caudal) (Fig. 1). The cranial face of each slice was photographed, and they were stored in 30% ethanol until sampled for histopathological analysis.

Mapping gross pathology. Digital images of the cranial face of each slice were uploaded onto a computer. In the 6 of 10 EIPH-affected horses in which there were clearly demarcated lesions of EIPH, the lesion was outlined and, using an annotation tool and computer software (Olympus FluoView software, Olympus America, Center Valley, PA), the mean percent area of affected lung was calculated. Also scored but not mapped, because the appropriate structures were not present in all samples. The scoring for each of the five changes ranged from 0 (not present) to 3 (severe).

Sampling for histopathology. Because lung slices varied in cross-sectional area, it was necessary to standardize the size of lung piece from which each sample was obtained. This size was based on the four caudalmost slices, which were the smallest. The remaining larger slices were then subdivided into pieces that roughly approximated this size (Fig. 1). A sample was then selected from each piece using the smooth fractionator technique (10, 17). Using this technique, a total of 1,400 samples (approximate size 1.5 cm²) were collected from EIPH-affected lungs, and 1,120 samples were collected from control horse lungs.

Histopathology. The lung samples were routinely processed, embedded in paraffin, and sectioned. Six-micrometer sections were placed on glass slides and stained with hematoxylin-eosin. A board-certified veterinary pathologist (K. Williams) evaluated the slides blindly, i.e., without knowledge of the horse or region of the lungs from which they were derived, and assigned a histopathological score based on three criteria previously established to be characteristic of EIPH (44): VR, H, and IF. Two other characteristic lesions, i.e., pleural/interlobular septal collagen and peri-airway collagen, were also scored but not mapped, because the appropriate structures were not present in all samples. The scoring for each of the five changes ranged from 0 (not present) to 3 (severe).

Data analysis. We analyzed four response variables: 1) the percentage of grossly visible lesions in each lung slice; 2) the mean sample score (MSS); 3) the percentage of samples with histological scores ≥ 0.5; and 4) the lesion score of affected samples. The percentage area of grossly evident EIPH lesions in each slice was compared using a three-factor ANOVA with random horse and fixed right and left lung and fixed slice number. Tukey’s honestly significant difference test was used for post hoc testing. Initial evaluation of data showed no statistical differences between histological scores of right and left lungs, so data were combined. To address issues of lesion distribution within the horizontal and vertical plane, samples were grouped into seven regions (Fig. 1). Dorsal samples from slices 1–4 became region D1, while ventral samples became region V1, and so forth. Because the caudalmost four slices reside only in the dorsal thorax, for slices 13–16, there is only region D4 and no corresponding ventral region. In each of these regions, we determined MSS for VR, H and IF. The MSS was the average of all scores for each lesion and included both normal (score 0) and diseased (scores 0.5–4.0) samples. In addition, we calculated the percentage of samples with sample scores ≥0.5 and the average score of samples with lesions, which we called mean lesion score (MLS). These three response variables were analyzed in a two-factor ANOVA (random horse, fixed region). Significance was determined as P < 0.05 and adjusted for multiple comparisons as necessary. Statistical analysis was by use of SAS version 9.1.3 (Cary, NC).
RESULTS

Gross pathology. In the control horses, there were no gross lesions visible on either the pleural surface of the lungs, or on the cut surface of the lung slices. In contrast, in all EIPH-affected horses, the pleural surfaces of the dorsocaudal lung regions were discolored, dark blue-black to brown. Similar discoloration extended cranially along the dorsal pleural surfaces to varying extents in many of the horses. In some of the horses, variably-sized foci of firm lung were palpable within the lung parenchyma, beneath the pleura. No gross cardiac abnormalities were noted. Postfixation, the cut surface of the lung slices revealed a variety of changes within the deeper lung that were not visible from the external surface, and which have not been reported before in association with EIPH. Interspersed within the normal fixed lung, there were multiple pale off-white foci. These foci were variable in their size and shape, ranging from discrete masslike formations (up to 5 cm) to curvilinear bands (Fig. 2). In 6 of the 10 horses, these foci were sufficiently well-demarcated from the surrounding grossly normal lung to be outlined with confidence (Fig. 2). In these horses, the mean percent area of each slice affected with gross EIPH lesions increased significantly in the craniocaudal direction from $4.3 \pm 5.5\%$ (least squares mean $\pm$ SE) in slice 1 to $50.5 \pm 6.1\%$ in slice 16 (Fig. 3).

Histopathology. No evidence of remodeling was evident within the lungs of the control horses. In general, the histopathology findings within the EIPH-affected horse lung were similar to those our laboratory previously reported (44). Briefly, all horses had varying degrees of a combination of five histological findings: vascular remodeling, H accumulation, IF, and pleural/interlobular septal fibrosis. The aforementioned grossly visible foci of parenchymal consolidation and pallor histologically consisted of discrete regions of interstitial edema and fibrosis, often with numerous interspersed small arterioles interpreted as neovascularization (Fig. 4). The presence of this edema was unrelated to the age of the animal or the duration of time since last race.

To map VR, it was critical to be able to reliably distinguish pulmonary arteries from veins. Pulmonary arteries and veins were identified based on their anatomic location and histological features. Pulmonary arteries follow the conducting airways and have a well-developed tunica media, with an internal and external elastic lamina. The large branches of pulmonary veins...
are also present within the bronchovascular bundle, while the smaller branches, those remodeled in EIPH, with an OD of 100–200 μm, that are the basis for the VR scoring do not follow the conducting airways. These veins are thin-walled and have a single elastic lamina separating a thin tunic media from the adventitia (Fig. 5). The histology of VR in EIPH-affected horses varied with the overall severity of lung remodeling. Veins with VR scores of 1 and 2 had mild-to-moderate increases in adventitial collagen, respectively (Fig. 5), while those veins with the highest scores (3) had prominent and dense collars of adventitial collagen (Fig. 5). Small numbers of such veins also had significant medial smooth muscle thickening and occasionally reduction of the lumen diameter associated with intimal collagen accumulation (Fig. 5).

**Distribution of histopathological lesions.** MSS for VR, H, and IF were always highest in the most caudal region, i.e., D4 and decreased progressively in a caudal-to-cranial direction. In the case of VR (Fig. 6, top), ventral region MSS were always significantly less than in the corresponding dorsal region. Both dorsally and ventrally, MSS decreased significantly between the caudal and cranial regions. This combination of gradients resulted in the biggest difference between region D4 (MSS = 1.32 ± 0.19; mean ± SE) and region V1 (MSS = 0.15 ± 0.18). Statistically identical MSS gradients were obtained for H (Fig. 6, middle) in which the MSS for D4 and V1 were 1.24 ± 0.17 and 0.16 ± 0.16, respectively. The caudal-to-cranial decrease in MSS was also observed for IF (Fig. 6, bottom), but, unlike VR and H, there were no significant differences between corresponding dorsal and ventral regions.

Calculation of MSS score used all samples taken from a particular region, including those with a score of zero. For this reason, a difference between regions could be due to either a difference in the number of samples with lesions and/or a difference in lesion severity in affected samples. To address these two possibilities, we calculated the percentage of samples with a sample score greater than zero and the MLS of these samples. For VR, H, and IF (Fig. 7), the percentage of samples with lesions followed a very similar distribution to MSS. In addition to the regional differences in percentage of affected samples, there were also significant regional differences in
Fig. 6. Mean sample score of each of the four dorsal (solid bars) and three ventral (shaded bars) regions. Data are shown for VR (top), hemosiderin (H) accumulation (middle), and interstitial fibrosis (IF; bottom). Values are means ± SE; n = 10 horses. a Significant difference between dorsal and ventral region. b Significantly different from region D4. c Significantly different from region V3.

Fig. 7. Percentage of affected samples of each of the four dorsal (solid bars) and three ventral (shaded bars) regions. Data are shown for VR (top), H accumulation (middle), and IF (bottom). Values are means ± SE; n = 10 horses. a Significant difference between dorsal and ventral region. b Significantly different from region D4. c Significantly different from region V3.
MLS (Fig. 8) that followed the same caudal-to-cranial gradient, but there were no statistically significant differences between dorsal and ventral regions.

To address the issue of colocalization of VR, H, and IF, we first searched the data and then statistically compared the percentage of samples with these lesions within each region. Searching of the data revealed that, in 96/1,395 (6.9%) samples, VR was present without H, but only when VR \( \leq 1.0 \). H was present without VR in 87/1,395 (6.2%) samples. However, in only 4/1,395 (0.3%) samples were there IF without VR, and IF never existed without H. In contrast, there were numerous samples, particularly in the cranial and ventral regions, where VR and H existed without IF (Fig. 9). Statistical comparisons found no differences in the percentage of VR- and H-affected samples in any region, and the percentage of VR-, H-, and IF-affected samples did not differ statistically in region D4. However, more cranially and ventrally, the percentage of IF-affected samples became progressively less than the percentage of VR- and H-affected samples. This was particularly apparent in regions D1, D2, V1 and V2.

**DISCUSSION**

Although EIPH has been documented in a variety of species, including humans, dogs, and camels, it is most common in horses. (1, 4, 8, 9, 11, 15, 31, 40). In racing Thoroughbreds, where the prevalence of EIPH approaches 80%, it is associated with impaired performance (12). Despite its high prevalence in horses, and the suggestion that it occurs in a variety of species, there is very little understanding of EIPH pathogenesis. The earliest in-depth investigation of lung pathology in EIPH-affected horses (26–28) documented the caudodorsal lung as most commonly affected (26). At that time, blood flow was thought to be gravity dependent, and so a variety of hypotheses were proposed to explain the apparently counterintuitive development of EIPH in the most dorsal part of the lung, including preexisting airway inflammation (7, 28). Concussive limb forces referred to the thoracic cavity during running have also been proposed as part of the pathogenesis (28, 35, 36). Discovery of the fractal distribution of blood flow in the horse lung, and documentation of the very high vascular pressures achieved in the equine lung during exercise (13, 22, 24, 25, 34), provided critical information in the understanding of EIPH. In the resting horse, pulmonary blood flow increases in a dorsal and somewhat in a caudal direction. During exercise, blood flow increases yet further in a dorsal direction, but with no consistent change in caudal direction (2). This knowledge of the distribution of blood flow supported the idea that exercise-induced capillary hypertension might directly lead to rupture of alveolar capillaries within the dorsocaudal lung without the necessity of coincident processes (42). Pressure-induced stress failure of capillaries can, however, have both physiological (e.g., exercise-induced capillary hypertension) and pathological (e.g., mitral stenosis and pulmonary venoocclusive disease) causes (41), and recent work in our laboratory suggests that both may be critical to the development of EIPH. In a study comparing six regions of the lung (3 from the dorsal lung, cranial to caudal; 3 from the ventral lung, cranial to caudal) from seven EIPH-affected horses (44), we observed extensive pulmonary pathology, including VR, H accumulation, and lung fibrosis. The combination of VR and H suggested that small-
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The present study is the first to systematically and in an unbiased manner sample the equine lung to map the distribution of EIPH lesions. The numbers of EIPH-affected animals and age-matched controls, fixation of the lungs under pressure, and use of a design-based sampling technique recommended for quantitative assessment of lung structure by the American Thoracic Society and European Respiratory Society (16) are particular strengths of the study. The Smooth Fractionator technique of Systematic Uniform Random Sampling (10) has been validated for sampling the entire lung or subcompartments of the lung (10, 17) and is recommended for acquisition of unbiased samples when mapping the occurrence of both random (isotropic) processes (e.g., EIPH pathology) and non-random (anisotropic) features (e.g., blood vessels), as was necessitated by the hypotheses in this study (16). The efficiency of this sampling technique is designed to keep the numbers of samples low, while still maintaining the accuracy of the results (16). We restricted our sampling of the subject animals to the caudal 24 cm of lung. This region was selected based on a previous study of EIPH horses that suggested that the disease did not extend appreciably cranial to this level (44). Even so, 2,520 individual tissue sections were examined from the two populations of horses, making it the largest histological survey of the equine lung to date.

There are several weaknesses of our investigation. First, all EIPH-affected horses had been retired from racing because of the severity of bleeding during racing. While it would have been ideal to examine some horses earlier in their racing career to investigate the progression of EIPH lesions, the reliance on donation of animals made this impossible. Furthermore, use of age-and breed-matched controls would be ideal, but this is cost prohibitive. Despite this, we obtained and included four such animals with orthopedic problems, which precluded any strenuous exercise. The lung histology of these animals was indistinguishable from the other controls. The EIPH lesions were scored subjectively rather than being quantified morphometrically, as the latter approach would have been time and cost prohibitive; however, all samples were scored by the same pathologist (K. Williams), who was blinded to the source of the sample.

The majority of the gross and subgross pathology findings in the present study are consistent with previous descriptions. These changes consisted of discoloration of the pleura over the dorsocaudal lung, dark brown foci of H, and thickening of the interlobular septa (26, 29, 44). In addition, however, we observed grossly evident masslike and curvilinear pale foci within the lung parenchyma of what was histologically determined to be interstitial edema. Such lesions have not previously been reported in equine EIPH (see below). Our mapping of the spatial distribution of subgross lesions in a subset of the most grossly abnormal lungs confirms the caudal lung as the site most extensively affected in the disease (26–29, 44). The severity of the lesions was not dependent on the age of the horse. More than 40% of the cut surface area of each of the four caudal lung slices had grossly evident pathology. This percentage decreased progressively in a cranial direction, so that each of the three most cranial slices had <5% involvement. This distribution is consistent with the results of O’Callaghan et al. (27), who reported 71% of grossly evident H accumulation was present within the dorsocaudal lung.
Most of the histopathological lesions we observed in this extensive examination of US horses were similar to those our laboratory recently described in a limited number of tissue samples from EIPH-affected animals in Singapore (44). In both of our studies, we documented a characteristic constellation of lesions within the lungs that consisted of VR, H accumulation, IF, and septal and pleural fibrosis. We have not included the septal and pleural fibrosis in the present analysis, as these structures cannot be expected to be present in all slides.

To address our hypotheses, statistical analysis was limited to VR, H, and IF. We tested our first hypothesis (VR follows the known preferential distribution of blood flow in the lung) by statistically comparing VR MSS between regions. The score was lowest in the most cranioventral lung region (V1) and greatest in the most caudodorsal region (D4). In the vertical direction, scores of regions D1, D2, and D3 were significantly greater than those of V1, V2, and V3, respectively. Statistically significant increases also were found in the horizontal plane (Fig. 6), with scores increasing between D1 and D4 and between V1 and V3. This distribution of VR supports our first hypothesis: both blood flow and VR increase vertically (dorsal in the horse) and horizontally (i.e., within the same isotovolumetric field) so that the caudodorsal region, which receives the most blood flow, has the greatest MSS for VR.

Because MSS includes samples with and without VR, we needed to know if regional differences were due to differences in the percentage of samples with VR or in VR severity (i.e., MLS). The percentage of affected samples significantly increased in the same vertical (dorsal) and horizontal (caudal) manner as MSS. By contrast, MLS significantly increased somewhat in the horizontal (caudal) plane, but not in the vertical direction. Our data suggest, therefore, that two different processes may be at work in EIPH: one determining the frequency of lesions within a region, the other determining lesion severity.

Information on blood flow distribution in horse lungs is based on fluorescent microsphere distribution in the lungs of four horses studied at rest and during exercise. Regional blood flow increases consistently in the vertical plane (2, 13). In the present study, this is also true of the percentage of samples with VR or in VR severity (i.e., MLS). The percentage of affected samples significantly increased in the same vertical (dorsal) and horizontal (caudal) manner as MSS. By contrast, MLS significantly increased somewhat in the horizontal (caudal) plane, but not in the vertical direction. Our data suggest, therefore, that two different processes may be at work in EIPH: one determining the frequency of lesions within a region, the other determining lesion severity.

Unlike lesion frequency, VR severity lacked a vertical gradient (Fig. 8), which suggests it may not be solely a consequence of variation in blood flow, but rather the result of a stimulus applied more uniformly to the veins. Although blood flow varies between lung regions, the exercise-associated pulmonary hypertension is transmitted to the entire lung. Furthermore, the elevated pulmonary arterial pressure [96.5 mmHg (25) to 101.8 mmHg (21)] is not due to increased arterial resistance, but rather is a consequence of increased left atrial [70 mmHg (19)] and pulmonary venous pressures [70.1 mmHg, pulmonary artery wedge pressure (19)]. For this reason, we propose that VR severity is primarily a consequence of the elevated venous transmural pressure occurring during intense exercise than the regional variation in flow. If one considers the racing horse has a heart rate of 220 beats/min (3.7 beats/s), the filling time for a stroke volume of 1.5 liters is ~0.13 s (33)! Therefore, it is not unreasonable to consider that the VR that is central to EIPH pathogenesis is, in part, the result of the very high filling pressures needed to sustain such physiological demands.

In this and in previous investigations of EIPH, lesions were absent in the most ventral and cranial parts of the lung tissue that we examined. Examination of the data on distribution of blood flow in exercising horses, however, suggests a possible explanation that is congruent with our hypothesis that the magnitude of flow initiates VR and the magnitude of vascular pressure determines the severity of the lesions; indeed, high pulmonary intravascular pressure is a known stimulus for VR (5, 18).

In the four horses in which blood flow distribution was measured (2), there are parts of the dorsal lung in which flow exceeds that in any part of the ventral lung. Perhaps VR begins in these very-high-flow regions of the dorsal lung in response to the associated focal high pressures. In the absence of these very-high-flow regions, such extremes of pressure do not exist ventrally.

Our second hypothesis is that VR is essential for the development of other lesions of EIPH. If this is true, H and IF cannot occur without VR. We tested this hypothesis by examining the colocalization of VR, H, and IF. In support of our hypothesis, VR occurred alone, in the absence of H, in 6.9% of samples. The distributions of H MSS (Fig. 6), percentage of H-affected samples (Fig. 7), and H MLS (Fig. 8) were virtually identical to those of VR. Furthermore, the percentage of samples with VR and H was not statistically different in any region (Fig. 9), and only a small percentage of samples contained H without VR. It is not surprising that we found H alone, given that its formation is at the site of hemorrhage, which may be from capillaries not immediately adjacent to their remodeled vein.

With regards to IF, only in the most dorsocaudal region (D4) there was no significant difference in the percentage of samples with IF, H, and VR, reflecting the full expression of EIPH pathology in this region. In all other regions, the percentage of samples with IF was significantly less than those with VR or H. In the region D4, which had the most extensive and severe VR and H, IF was most extensive. As VR and H decreased in extent, so did IF. These data strongly suggest that IF is a sequel to the initial lesions of VR and H.

The delayed development of IF relative to VR can be explained by the following sequence of events: increased transvascular fluid flux is expected to be greatest in the caudodorsal lung during exercise as a consequence of the high regional blood flow in the CD lung. VR then further compounds transvascular fluid flux, interstitial edema, and fibrosis (6, 38, 39).
Regions of lung with extensive pulmonary edema and fibrosis have not previously been described in EIPH-affected horses. During intense exercise, the equine lung has been calculated to move ~10 l/min of fluid from the vascular lumen (39), yet despite this remarkable fluid movement, racing horses do not develop appreciable clinically apparent pulmonary edema. While the exact site of this increased fluid flux has not been documented, the hydraulic conductivity of small pulmonary veins and arteries is greater than that of alveolar capillaries (30). For this reason there may be high fluid flux in the regions that have undergone VR. Our horses had not raced for weeks before euthanasia, so the finding of edema was surprising, and its cause is unknown. However, the edema was only present in regions of extensive VR and fibrosis. The geometry of the site of pulmonary edema present in the most severely affected EIPH lungs, with their discreet borders delineating affected from more normal lung, suggests that, in these regions, local VR of small-caliber veins (100–200 μm OD) was severe enough to elevate pulmonary microvascular hydrostatic pressure at rest sufficiently to cause the edema. Local lymphatic drainage may also have been compromised by the fibrosis. It seems unlikely that increased vascular permeability was the cause of the edema, because there was no evidence of local acute inflammation. Overall, it is logical that the edema forms at these sites where transvascular fluid flux, caused by the microvascular hydrostatic pressure and wall damage, is sufficient to exceed lymphatic clearance.

In summary, our data suggest that anatomic and physiological factors inherently associated with the caudodorsal lung favor remodeling of small intrapulmonary veins (100–200 μm OD). The similarity of the spatial distribution of blood flow, VR, and H supports our hypothesis that high rates of blood flow and vascular pressures underpin the VR, and this lesion is central to the pathogenesis and progression of EIPH.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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