Venous Occlusion Accompanies Bleeding, Hemosiderosis, and Fibrosis in Horses With Exercise-Induced Pulmonary Hemorrhage

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The caudodorsal lung receives high blood flow during exercise and is the site of lesions of exercise-induced pulmonary hemorrhage (EIPH). This leads to regional pulmonary venous fibrosis and obstruction, which is accompanied by marked hemosiderosis and fibrosis of the interstitium, the interlobular septa, and the walls of airways and pulmonary arteries. Authors' addresses: Department of Large Animal Clinical Sciences (Derksen, Robinson, DeFeijter-Rupp) and Department of Pathobiology and Diagnostic Investigation (Williams), College of Veterinary Medicine, Michigan State University, East Lansing, MI 48824; Marion duPont Scott Equine Medical Center, Virginia-Maryland Regional College of Veterinary Medicine, PO Box 1938, Leesburg, VA 20176 (Pannirselvam); and Equine Centre, Veterinary Clinic and Hospital, The University of Melbourne, 250 Princes Hwy, Werribee 3030, Australia (Steel); e-mail: derksen@cvm.msu.edu. © 2007 AAEP.

1. Introduction

Exercise-induced pulmonary hemorrhage (EIPH) occurs in the majority of racehorses,1–3 and when severe, reduces performance.4 Despite its common occurrence, there is a poor understanding of the pathogenesis of EIPH. Currently, the most widely accepted hypothesis for the pathogenesis of EIPH is exercise-induced pulmonary hypertension, resulting in alveolar capillary wall stress failure.5 However, this hypothesis does not account for the lesions reported in EIPH, i.e., fibrosis, and bronchial circulation proliferation.6,7

This study was performed to further evaluate and quantify the lung lesions of EIPH in adult racing Thoroughbreds. Our histologic findings confirmed the presence of fibrosis, hemosiderin, and bronchial circulation angiogenesis; in addition, we identified, heretofore unreported, pulmonary vascular changes. Specifically, we documented morphologic evidence of lesions characteristic of pulmonary venous hypertension. These lesions bear striking similarity to those of pulmonary veno-occlusive disease in humans. Based on these findings, we suggest a novel pathogenesis for EIPH. We propose that regional veno-occlusive remodeling, especially within the caudodorsal lung fields, underlies the pathogenesis of EIPH.

2. Materials and Methods

Five adult Thoroughbred racehorses 5–7 yr of age, with a history of repeated episodes of post-race ep-
staxis, were euthanized for this reason. Six sections were collected from both lungs representing the cranial, middle, and caudal region of the dorsal and ventral lung. The 60 sections of lung were routinely processed and stained using hematoxylin and eosin, Masson’s trichrome, Prussian blue, Verhoef-Van Gieson, and Picosirius red (PR) stains. Each of the slides was assigned a histopathologic score (HS) based on five criteria: interstitial fibrosis; amount of hemosiderin; interlobular septal fibrosis; and vascular (arterial and venous) wall thickness. Hemosiderin was quantified using Prussian blue–stained sections, and collagen in airway, vein, artery walls, and the pulmonary interstitium and interlobular septa was morphometrically quantified on PR-stained slides, using computer software.a

3. Results

Gross Pathology

The gross lung lesions were similar to those described in previous reports.8 Both right and left lungs of all of the animals had numerous dark brown to blue-black foci along the dorsal visceral pleura of the lungs. These foci were most densely distributed within the caudodorsal field of both lungs.

Histopathologic Scoring

Twenty-two of 60 (37%) sections were judged to be histologically normal; 30/60 (50%) had moderate changes, whereas 8/60 (13%) had severe changes. The average HS was highest (8.4) within the caudodorsal lung field and lowest (0.2) in the cranioventral lung. The mean HS of the right and left lung did not differ significantly.

Histopathology

The spectrum of major histologic changes in the affected regions of lung consisted of fibrosis, hemosiderin accumulation, and vascular remodeling. This constellation of changes was consistently distributed at four major sites within the lung: alveolar interstitium, in the perivascular and perilobular regions, subpleurally, and in association with the interlobular septa. Hemosiderin accumulation was abundant within the most severely affected regions of the EIPH-affected lungs. The hemosiderin co-localized with the fibrosis in the four lung regions noted above. Marked vascular remodeling, involving the venous and arterial systems, was found within the most severely affected regions of the EIPH lungs. In sections with the highest HS, there were numerous thick-walled vessels within the pleura and interlobular septa. Throughout the affected regions, most intralobular veins were surrounded by a prominent collar of mature collagen, and in Verhoef-Van Geison–stained sections, the collagen could be seen to be interposed between the external elastic lamina and the lumen, often resulting in a markedly reduced lumen in the affected veins.

Morphometric Analysis

Compared with lung sections with the lowest HS, lung sections with the highest HS had a significant (p < 0.05) increase in hemosiderin and in collagen in the wall of the airway, vein, artery, intralobular septa, and the interstitium. The vascular lumens were also decreased in size, with the mean radius of vessels in the affected areas reduced by >50%.

4. Discussion

In this study, we described heretofore unreported pulmonary vascular lesions. These lesions are strikingly similar to those described for veno-occlusive disease in people.9 Throughout the affected regions, a prominent collar of mature collagen surrounded most intralobular veins, and vascular lumens were significantly reduced. Similar changes were found in pulmonary arteries. Humans with veno-occlusive disease also have pulmonary hemosiderosis and even hemoptysis.10 Thus, veno-occlusive disease is associated with pulmonary hemorrhage and hemosiderosis. In exercising horses, venous occlusion is expected to raise pulmonary capillary pressure, leading to EIPH.

An important finding of this study is that hemosiderin was co-localized with the fibrotic and vascular lesions. In humans, pulmonary diseases that are characterized by lung bleeding and hemosiderosis often also have fibrosis.11 The pathologic changes reported here suggest that venous occlusion may underlie bleeding, hemosiderosis, and fibrosis in horses with EIPH.

This research was supported by the Grayson-Jockey Club Research Foundation and the Matilda R. Wilson Endowment. The authors thank Dr. Tan Yang for providing case material and D. Glen and N. Kasmuri for technical assistance.

References and Footnote


*MicroSuite5 Biological Software, Olympus America, Center Valley, PA 18034.*