

Pulmonary hypertension and right-sided heart failure in an adult llama with hepatic disease

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RUMINANTS

Case Description—A 13-year-old llama was examined because of lethargy, inappetence, and syncope.

Clinical Findings—Physical examination revealed muffled heart and lung sounds and peripheral edema. Clinicopathologic abnormalities included lymphopenia, hyperglycemia, prerenal azotemia, mild hyponatremia, mild hypoalbuminemia, and high γ -glutamyltransferase and creatine kinase activities. On ultrasonography, the liver appeared hyperechoic and ascites and pleural effusion were seen. Echocardiography revealed severe dilatation of the right atrium, right ventricle, and pulmonary artery; severe tricuspid regurgitation; and high right ventricular systolic pressure consistent with right-sided heart failure secondary to pulmonary hypertension.

Treatment and Outcome—Treatment with furosemide was attempted, but because of failing health, the llama was euthanized 4 weeks later. Macronodular cirrhosis of the liver, glomerulonephritis, and intimal fibrosis and medial hypertrophy of muscular pulmonary arteries were seen on histologic examination of postmortem specimens.

Clinical Relevance—Findings in this case were similar to those reported for human patients with portopulmonary hypertension secondary to hepatic cirrhosis. Pulmonary hypertension secondary to hepatic disease should be considered in the differential diagnosis of right-sided heart failure. (*J Am Vet Med Assoc* 2006;228:756–759)

A 13-year-old 148-kg (326-lb) female llama was examined because of a 2- to 3-week history of lethargy, inappetence, and syncope. The owner had dewormed the llama with an avermectin-containing product 1 week prior to examination. The diet consisted of mixed grass pasture, a pelleted feed supplement formulated for llamas, and a mineral supplement formulated for llamas. The llama also had access to a salt block. The llama was reported to be grazing but ate only about a quarter of its normal daily intake of the pelleted supplement.

On initial examination, body condition appeared adequate (body condition score of 7 on a scale from 1 to 10¹). Rectal temperature (39.2°C [102.6°F]; reference range,² 37.5° to 38.9°C [99.5° to 102.0°F]), heart rate (92 beats/min; reference range,² 60 to 90 beats/min), and res-

piratory rate (48 breaths/min; reference range,² 10 to 30 breaths/min) were high. Thoracic auscultation revealed muffled heart and lung sounds bilaterally. No jugular vein distension or pulsation was evident during physical examination; however, llama jugular veins are not easily examined because of the thick layer of skin and fleece over the jugular furrow. The llama had ventral subcutaneous edema extending from the pubis to the thoracic inlet. No other physical abnormalities were identified.

Initial testing included a CBC, serum biochemical profile, and urinalysis. The only hematologic abnormality was lymphopenia (0.4×10^3 cells/ μ L; reference range,² 0.7 to 4.8×10^3 cells/ μ L). Serum biochemical abnormalities included hyperglycemia (194 mg/dL; reference range,² 76 to 176 mg/dL), high urea nitrogen concentration (42 mg/dL; reference range,² 9 to 36 mg/dL), high creatinine concentration (4.2 mg/dL; reference range,² 0.9 to 2.8 mg/dL), hyponatremia (144 mmol/L; reference range,² 148 to 158 mmol/L), hypoalbuminemia (2.3 g/dL; reference range,² 2.9 to 5.0 g/dL), high γ -glutamyltransferase activity (78 U/L; reference range,² 3 to 28 U/L), and high creatine kinase activity (596 U/L; reference range,² 0 to 137 U/L). Results of the urinalysis were within reference limits; urine specific gravity was 1.031 (reference range,² 1.010 to 1.048).

The initial problem list included inappetence, peripheral edema, muffled heart and lung sounds, prerenal azotemia, cholestasis, and high muscle enzyme activities. The inappetence was thought to be attributable to a primary illness. Possible mechanisms for the peripheral edema that were considered included decreased plasma colloid oncotic pressure, increased vascular permeability, increased hydrostatic pressure, and decreased lymphatic drainage.³ Although the llama was hypoalbuminemic, the albumin concentration was not considered low enough to account for the edema.⁴ The most likely cause of the muffled heart and lung sounds, given the peripheral edema, was pleural effusion. The high γ -glutamyltransferase activity was consistent with cholestasis, and differential diagnoses for cholestasis that were considered included anorexia, hepatic lipidosis, biliary obstruction, and primary or secondary hepatic disease.

Additional testing included ultrasonography of the liver, abdomen, and thorax and echocardiography. Measurement of serum sorbitol dehydrogenase activity was considered as a method for determining the extent of any hepatocellular injury but was not available locally.

Ultrasonographically, the liver appeared hyperechoic, which was consistent with hepatic fibrosis, and a large amount of free fluid was evident in the peritoneal cavity. Abdominocentesis yielded a clear color-

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less fluid with a specific gravity of 1.010, total protein concentration < 2.5 g/dL, PCV < 2%, and total nucleated cell count of 83 cells/ μ L (85% large monocytoid cells, 4% small lymphoid cells, and 11% neutrophils), which was identified as a transudate. Pleural effusion was evident during ultrasonography of the thorax.

Echocardiography revealed severe dilatation of the right atrium, right ventricle, and pulmonary artery (Figure 1). Flattening and paradoxical motion of the interventricular septum were present, indicative of high pressures within the right side of the heart. Color-flow Doppler ultrasonography revealed severe tricuspid regurgitation. Peak velocity of the regurgitant flow, measured by means of continuous-wave Doppler ultrasonography, was 4.8 ms^{-1} , which was equivalent to a pressure gradient of 90 mm Hg. Given the size of the right atrium and the fact that in patients with ascites or pleural effusion secondary to right-sided heart failure, right atrial pressure will be at least 10 to 15 mm Hg,⁵ right atrial pressure was estimated to be at least 10 mm Hg (reference range,² 2.6 ± 0.7 mm Hg). Hence, peak right ventricular systolic pressure was estimated to be at least 100 mm Hg ($90 + 10$ mm Hg). The velocity of flow through the right ventricular outflow tract was normal, which ruled out pulmonic stenosis as the cause of the high right ventricular systolic pressure. The high pressure in conjunction with enlargement of the pulmonary artery was consistent with a diagnosis of pulmonary hypertension with secondary right-sided heart failure. However, the llama did not have any history of respiratory tract disease, and no signs of respiratory tract disease were evident on physical examination. Arterial blood gas analysis revealed an O_2 saturation of 88.3% (reference range,⁶ > 90%).

Thoracic radiography and percutaneous liver biopsy were offered as additional methods for evaluating the liver and lungs, but given the llama's perceived poor prognosis, the owner elected to not pursue further testing. Treatment with furosemide (1 mg/kg [0.45 mg/lb], IM, q 24 h) was instituted, and the owner reported that the llama's appetite and activity level initially improved. However, 4 weeks after the initial examination, the owner reported that the llama's condition had deteriorated and that the llama was no longer able to stand and requested that the llama be euthanized.

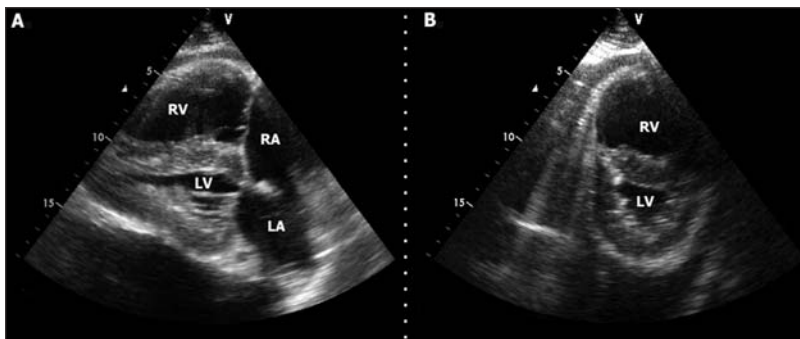


Figure 1—Right parasternal long-axis (A) and short-axis (B) ultrasonographic views of the heart of a 13-year-old llama examined because of ascites and pleural effusion. The right atrium (RA) and right ventricle (RV) appear dilated, whereas the left atrium (LA) and left ventricle (LV) appear small and underfilled. The interventricular septum was flattened in systole and diastole.

At the time of euthanasia, the llama weighed 115 kg (254 lb), or 33 kg (73 lb) less than at the time of initial examination. Gross postmortem findings included ventral subcutaneous edema, perirenal edema, and perirectal edema. Approximately 6 L of amber, translucent fluid containing fibrin clots was found in the peritoneal cavity. Approximately 2 L of similar-appearing fluid was found in the pleural cavity. The liver was overlaid by fibrin strands, contained multiple 2- to 3-cm-diameter nodules, and was firm on cut surface. The omentum and serosa of the gastrointestinal tract were congested with multifocal telangiectasia and lymphangiectasia. No gross lesions were observed in the lungs, and sections of lung floated in formalin. The right side of the heart was enlarged. Total cardiac weight was 561.7 g, the left ventricle and interventricular septum weighed 279.7 g, and the right ventricle weighed 118.0 g. The ratio of left ventricle and interventricular septum weight to right ventricle weight was 2.4. Circumference of the aortic valve was 7.6 cm, and circumference of the pulmonic valve was 10.0 cm; the ratio of aortic valve circumference to pulmonic valve circumference was 0.76. Circumference of the left atrioventricular valve was 12.4 cm, and circumference of the right atrioventricular valve was 15.8 cm; the ratio of left atrioventricular valve circumference to right atrioventricular valve circumference was 0.78. Left ventricular thickness was 1.7 cm, interventricular septal thickness was 1.7 cm, and right ventricular thickness was 0.8 cm. Reference ranges for these measurements in llamas were not available, but in dogs, the reference range⁷ for the ratio of left ventricle and interventricular septum weight to right ventricle weight is 3.3 ± 0.3 , the ratio of aortic valve circumference to pulmonic valve circumference is 0.99 ± 0.09 , and the ratio of left atrioventricular valve circumference to right atrioventricular valve circumference is 0.78 ± 0.09 . Thus, gross postmortem findings for the llama were consistent with right ventricular hypertrophy and dilatation of the pulmonary trunk.

Sections of heart, lung, liver, kidney, small intestine, and large intestine were stained with H&E stain and examined. The lungs were congested, and intimal fibrosis and medial hypertrophy of muscular pulmonary arteries were seen (Figure 2). Hepatic abnormalities included biliary hyperplasia and fibrosis subdividing multiple large proliferative nodules of hepatocytes (Figure 3). Examination of kidney specimens revealed multifocal cystic dilatation of renal tubules and thickening of the Bowman capsule and glomerular basement membrane, and examination of intestinal specimens revealed telangiectasia, lymphangiectasia, and edema of the tunica serosa and mesentery. Histologic diagnoses included hepatic fibrosis characterized by biliary and macronodular hyperplasia (macronodular cirrhosis), glomerulonephritis, and medial hypertrophy of muscular pulmonary arteries.

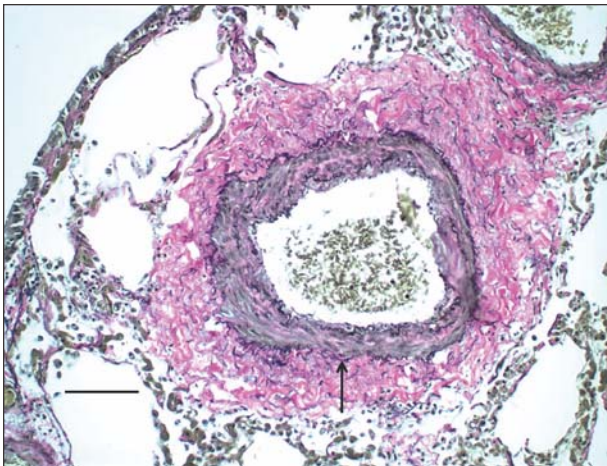


Figure 2—Photomicrograph of a section of lung from the llama in Figure 1. Notice the intimal fibrosis and medial hypertrophy of the muscular pulmonary arteries (arrow). Verhoeff elastic stain; bar = 100 mm.

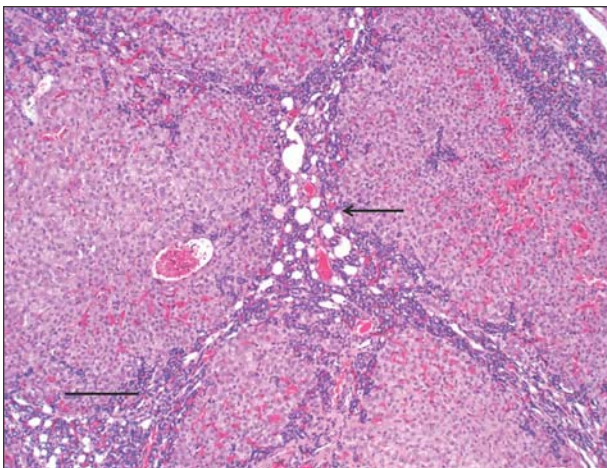


Figure 3—Photomicrograph of a section of liver from the llama in Figure 1. Notice the biliary hyperplasia (arrow) and fibrosis subdividing multiple large proliferative nodules of hepatocytes. H&E stain; bar = 100 mm.

Discussion

The cause of the right ventricular hypertrophy and right-sided heart failure in the llama described in the present report was most likely pulmonary hypertension. The absence of any signs of clinically important pulmonary parenchymal disease and the severity of hepatic fibrosis suggested that the hepatic disease was primary and that pulmonary hypertension developed secondary to hepatic disease.

Pulmonary hypertension is a well-documented sequela to hepatic disease in human patients.⁸⁻¹² Portopulmonary hypertension can occur in patients with advanced hepatic disease and is characterized by pulmonary arterial hypertension and portal hypertension.⁹ Signs of portopulmonary hypertension in humans include exertional dyspnea, orthopnea, chest pain, fatigue, leg edema, and syncope.⁹ Affected patients usually have normal O₂ saturation at rest but have worsening hypoxemia with exercise. The underlying pathophysiology is unknown but is thought to involve the buildup of circulating vasoactive substances not fil-

tered by the diseased liver.¹⁰ Pulmonary vascular histologic lesions identified in humans with portopulmonary hypertension are similar to those seen in patients with pulmonary arterial hypertension secondary to other causes and include plexiform arteriopathy, medial hypertrophy, intimal fibrosis, adventitial proliferation, and fibrinoid necrosis of small arteries.^{9,11} A clinical diagnosis of portopulmonary hypertension is made in humans on the basis of mean pulmonary arterial pressure > 25 mm Hg at rest, pulmonary vascular resistance > 120 dyne·s·cm⁻³, pulmonary capillary wedge pressure < 15 mm Hg, and portal pressure > 10 mm Hg.⁹ Treatment in human patients includes IV administration of prostacyclin. If mean pulmonary arterial pressure can be decreased to < 40 mm Hg, then liver transplantation is feasible.^{9,12}

Given that pressure in the pulmonary artery is equal to the pressure in the right ventricle during systole,³ it can be concluded that systolic pulmonary arterial pressure in the llama described in the present report was in excess of 100 mm Hg, indicating that mean pulmonary arterial pressure was in excess of 25 mm Hg. Pulmonary capillary wedge pressure was not measured in part because of the difficulty in passing a catheter through the multiple valves in the llama jugular vein and in part because of the owner's wish to not pursue further diagnostic testing. Arterial oxygen saturation in South American camelids is reported to be in excess of 90% even at an altitude of 3,300 m,⁶ and hypoxemia in the llama described in the present report was likely a result of alterations in pulmonary blood flow⁹ and increased activity associated with collection of a blood sample. Medial hypertrophy of the muscular pulmonary arteries was consistent with changes seen in human patients with portopulmonary hypertension, but the full complement of pulmonary vascular changes reported in people with portopulmonary hypertension⁹ was not observed. The underlying cause of the hepatic fibrosis remains unknown. The pattern of hepatic disease was not consistent with chronic passive hepatic congestion secondary to right heart failure (ie, centrilobular congestion and fibrosis) but was more diffuse.

The presence of ascites in the llama described in the present report was consistent with portal hypertension. However, portal pressure was not measured, and it is likely that the cause of the ascites in this patient was multifactorial. The severe enlargement of the right atrium and the tricuspid regurgitation were consistent with right-sided heart failure. However, right-sided heart failure typically results in formation of ascites with a relatively high protein concentration (> 2.5 g/dL) secondary to postsinusoidal portal hypertension.¹³ The high hydrostatic pressure causes increased leakage of hepatic lymph, which is usually a modified transudate. Presinusoidal portal hypertension, such as occurs with chronic hepatic fibrosis, increases hydrostatic pressure in the portal system, causing leakage of intestinal lymph, which typically has a low protein concentration (< 2.5 g/dL), resulting in transudative ascites.¹³ In this llama, hypoalbuminemia may have also contributed to the ascites.

Glomerulonephritis was not diagnosed clinically in the llama described in the present report. Although

the llama had high serum urea nitrogen and creatinine concentrations, urine specific gravity was indicative of prerenal azotemia and proteinuria was not detected. The ability to concentrate urine is lost when approximately 66% of nephrons are nonfunctional, and renal azotemia is not detected until approximately 75% of nephrons are nonfunctional.¹⁴ Hence, it is likely that the glomerulonephritis was not severe enough to cause loss of urine-concentrating ability in this llama. Renal failure (hepatorenal syndrome) is reported in human patients with hepatic cirrhosis, but renal failure occurs secondary to intense vasoconstriction of the renal circulation and not glomerulonephritis.¹⁵

In conclusion, pulmonary hypertension secondary to hepatic disease should be considered in the differential diagnosis of right-sided heart failure. To the authors' knowledge, this is the first report of pulmonary hypertension and right-sided heart failure associated with hepatic disease in a domestic animal.

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Selected abstract for JAVMA readers from the American Journal of Veterinary Research

Effects of phenylbutazone alone or in combination with flunixin meglumine on blood protein concentrations in horses

Shannon K. Reed et al

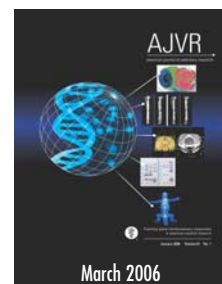
Objective—To assess effects of treatment with phenylbutazone (PBZ) or a combination of PBZ and flunixin meglumine in horses.

Animals—24 adult horses.

Procedure—13 horses received nonsteroidal anti-inflammatory drugs (NSAIDs) in a crossover design. Eleven control horses were exposed to similar environmental conditions. Treated horses received PBZ (2.2 mg/kg, PO, q 12 h, for 5 days) and a combination of PBZ and flunixin meglumine (PBZ, 2.2 mg/kg, PO, q 12 h, for 5 days; flunixin meglumine, 1.1 mg/kg, IV, q 12 h, for 5 days). Serum samples were obtained on day 0 (first day of treatment) and day 5, and total protein, albumin, and globulin concentrations were measured.

Results—1 horse was euthanized because of severe hypoproteinemia, hypoalbuminemia, and colitis during the combination treatment. Comparisons revealed no significant difference between control horses and horses treated with PBZ alone. There was a significant difference between control and treated horses when administered a combination of PBZ and flunixin meglumine. Correction for horses with values > 2 SDs from the mean revealed a significant difference between control horses and horses administered the combination treatment, between control horses and horses administered PBZ alone, and between horses receiving the combination treatment and PBZ alone. Gastroscopy of 4 horses revealed substantial gastric ulcers when receiving the combination NSAID treatment.

Conclusions and Clinical Relevance—Analysis of results of the study indicates the need for caution when administering a combination NSAID treatment to horses because the detrimental effects may outweigh any potential benefits. (*Am J Vet Res* 2006;67:398–402)



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