Overview of Bovine High-Mountain Disease

(“Brisket” disease, Big brisket, Dropsy, High-altitude disease, Pulmonary hypertension, Congestive right heart failure)

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Bovine high-mountain disease (BHMD) is characterized by a noncontagious swelling of edematous fluid in the ventral parasternal muscles (brisket region), the ventral aspect of the body including the abdomen, and the submandibular region in cattle raised in high-altitude regions (>5,000 ft [1,524 m]) in the western USA most commonly and substantially affecting Colorado, Wyoming, New Mexico, and Utah. It also affects cattle in mountainous ranges of the world, most commonly at elevations >6,500 ft (1,981 m) in western Canada and South America. BHMD affects cattle of all ages and breeds, but not necessarily equally.

BHMD is a result of pulmonary arterial hypertension induced by pulmonary hypoxia occurring at high altitude. Hypoxia-induced pulmonary arterial vasoconstriction and arterial hyperplasia reduce the diameter of the pulmonary arterioles, resulting in pulmonary hypertension and subsequent right ventricular (RV) hypertrophy. Without intervention to reduce the hypoxia-induced pulmonary hypertension, the disease will eventually progress to RV congestive/dilatory cardiac failure. Rarely, similar lesions have been described in severely stressed and parasitized sheep and deer. Etiologically similar hypoxia-related heart failure has also been described in chickens in the Andes Mountains and in people living at extreme elevations. The incidence in cattle on high mountain pastures averages 3%–5% with variations from 0.5%–10% but has been as much as 65% in a genetically susceptible calf crop. A 25% calf loss is not uncommon in the high elevations of Colorado and Wyoming.

Although most commonly associated with altitude, other genetic, physiologic, environmental, and toxic factors play important roles in disease development and progression. Any pulmonary disease, acute or chronic, that hinders pulmonary function can result in a hypoxic condition similar to altitude-induced BHMD.

Etiology:
Although many factors may contribute to the incidence of BMHD, the pathogenesis is directly related to the hypoxic condition that results from high altitude. Pulmonary vascular shunting is a normal physiologic response to hypoxic conditions and is seen in all animals. Strong responses are seen in cattle, horses, and pigs, whereas people, dogs, guinea pigs, and llamas are less responsive. These findings and the high incidence of disease in cattle indicate they are uniquely susceptible. The vasoconstriction mechanism of shunting is a way to divert unoxygenated blood to oxygen-rich regions of the lungs (dorsal aspect) and away from poorly oxygenated regions (ventral aspect). Exaggerated shunting in response to hypoxia, the anatomic pattern of the bovine lobulated lung, and the small lung-size/body-weight ratio all contribute to a severe loss of functional pulmonary capacity.

Pulmonary vascular shunting is initially mediated through pulmonary arteriole constriction in the acute stages of hypoxia. Vascular hypertrophy and thickening of the medial layers of the pulmonary arterioles (medial hypertrophy) and adventitial tissues occurs with chronic hypoxic exposure (>3 wk). Vascular remodeling leading to loss of peripheral pulmonary arteries also contributes to increased pulmonary resistance. This combination of events causes significant pulmonary hypertension, which leads to a progression of cardiac pathology: RV hypertrophy, followed by RV dilation, and finally right congestive heart failure (CHF).

This pathogenesis of exaggerated vasoconstrictive shunting, arterial medial and adventitial hypertrophy, and vascular obliteration resulting in pulmonary hypertension appears to be characteristic of some cattle and is highly heritable. Some cattle appear to be more naturally resistant to this process, both on an individual and breed basis. There is marked individual and interspecies variability in hypoxia-induced increases in pulmonary vascular resistance. The role of genetics in BHMD is supported by high familial incidence with marked variation in susceptibility between individual animals, breeds, and other species of animals. There is strong evidence that the susceptibility of cattle to hypoxia-induced pulmonary hypertension is inherited. In addition to underlying genetic predisposition, altered chemoreceptor activity or myocardial metabolism may also play a role. Acute viral or bacterial respiratory disease can exacerbate pulmonary hypoxia of high altitude, resulting in a rapid onset of RV failure.

Various range plants, both browse and non-browse types, have been associated with increased incidence of BHMD, but only locoweed has been experimentally shown to induce the disease. When consumed by cattle at high elevation, locoweed (certain Oxytropis and Astragalus spp that contain the alkaloid swainsonine) markedly increase the prevalence and severity of CHF, which develops relatively quickly (within 1–2 wk) with an incidence as high as 100%. Swainsonine, the toxin in locoweed, is excreted in milk, thereby predisposing nursing calves to developing CHF. Locoweed-poisoned cows often abort, and many develop severe hydrops amnii in addition to showing signs of BHMD. Locoweed poisoning directly contributes to increased pulmonary vascular resistance and hypertension; immunohistochemistry and electron microscopy studies have shown that poisoning causes severe swelling and cytoplasmic vacuolation of pulmonary intravascular macrophages and endothelial cells. The myocardium also is compromised by locoweed, seen as extensive vacuolation of the myocardial interstitial cells. Finally, swainsonine has systemic endocrine and paracrine effects due to altered glycoprotein metabolism, which may also contribute to the pathogenesis of BHMD.

Clinical Findings:

The clinical changes of RV CHF of high-mountain disease usually develop slowly over several weeks, commonly within the first 3–4 wk after cattle are moved from lower to higher elevations. This 3–4 wk period may be an average time, but clinical signs and death from pulmonary hypertension and right CHF have been seen within 24 hr after altitude exposure and have also been seen in animals that have lived in higher elevations for years. In those areas in North America where cattle spend summer and
fall grazing at high altitudes and return to lower elevations later in the fall, the disease is usually manifest in late summer and early fall and seems to be associated with weather and environmental conditions as seen in high elevations with cold nights and hot days. Pulmonary hypertension and right CHF seem to follow respiratory disease seen with these same climatic influences. In areas where cattle live year round at high altitudes, the disease incidence is greatest in late fall, winter, or early spring. Periods of severe cold or other environmental stress (eg, pregnancy, change in nutrition) appear to precipitate the onset of signs. Affected animals initially appear depressed and reluctant to move. As the syndrome progresses, subacute edema develops in the brisket region and extends cranially to the intermandibular space and caudally to the ventral abdominal wall. Pleural effusion and ascites are usually abundant. Marked distention and pulsation of the jugular veins are usually prominent. Appetite may be decreased. Profuse diarrhea may develop as a result of intestinal venous hypertension. Respiration is labored, and animals may appear cyanotic. As the disease progresses, affected cattle become more reluctant to move and may become recumbent. With forced exertion, severely affected animals may collapse and die. In the terminal stages, the animal is often anorexic, recumbent, and unable to rise. To the rancher and cattlemen, an animal experiencing "brisket disease" is most often characterized by severe brisket and abdominal edema and swelling, jugular enlargement and pulsation, bulging eyes, exophthalmos (secondary to venous congestion), ventral abdominal distention (ascites), bloating, recumbency or inability to travel with the herd, and profuse diarrhea.

**Lesions**

Generalized edema is especially severe in the ventral subcutaneous tissues, skeletal musculature, perirenal tissues, mesentery, and wall of the GI tract. Ascites, hydrothorax, and hydropericardium are consistent findings. Fluid characteristics include low cellularity and low to normal protein, consistent with a transudate secondary to cardiac failure. The liver lesions, due to chronic passive congestion, vary from an early “nutmeg” appearance to severe lobular and vascular fibrosis. The lungs may have varying degrees of atelectasis, interstitial emphysema, edema, and pneumonia. The heart has marked RV hypertrophy and dilatation; the cardiac apex is displaced to the left, making the enlarged heart appear round. The right atrium is often 2–3 times larger than the left and is flaccid. Pulmonary arterial thrombosis is a frequent finding. Microscopically, there is hypertrophy of the media of small arteries and arterioles in the lungs. Acute rupture of the pulmonary artery (aneurysm) secondary to the severe pulmonary hypertension is often seen as a reason for acute death without clinical signs of RV CHF.

**Diagnosis:**

There is no definitive diagnostic test for BHMD. A diagnosis may be based on clinical findings related to CHF in cattle kept at high altitudes. Body temperature and CBC are generally normal unless there is other underlying inflammatory pathology. Recent studies in elevations ≥9,000 ft (2,743 m) found body temperatures in calves experiencing pulmonary hypertension to be increased (>104°F [40°C]). This is hypothesized to be secondary to an increased metabolic demand and tachypneic response to the hypoxic condition. Thoracic auscultation may reveal a decreased intensity of breath sounds in the ventral thorax and muffled heart sounds if pleural effusion is present. The heart and respiratory rates are generally increased, and a systolic cardiac murmur may be auscultated if RV enlargement has resulted in right atrioventricular or pulmonic valve insufficiency. In end-stage CHF, a gallop rhythm is often detected. Although jugular distention is a characteristic clinical sign, an abnormal jugular pulse may or may not be seen. The common clinical pathologic changes are increases in hepatic enzymes, particularly AST and l-iditol dehydrogenase. Clinically affected animals may be azotemic because of decreased renal perfusion secondary to heart failure and dehydration/hypovolemia.
BHMD should be differentiated from other causes of CHF, including pericarditis, traumatic reticulo- pericarditis, cardiac lymphosarcoma, valvular endocarditis, viral or bacterial myocarditis, cardiomyopathy (nutritional, hereditary, or idiopathic), pulmonary arterial obstruction from embolic pneumonia, or chronic hypoxia and cor pulmonale due to other primary pulmonary disease. Brisket edema may not always be present in animals with peracute RV CHF; this can result in BHMD in calves being mistaken for acute viral or bacterial pneumonia.

**Treatment and Control:**

Affected animals should be moved to a lower altitude with minimal restraint, stress, and excitement. General supportive therapy, including diuretics, thoracocentesis, antibiotics, and appetite stimulators such as vitamin B complex, may be beneficial. Thoracocentesis is the single treatment that most dramatically improves an affected animal’s chance of survival. At high elevations, use of oxygen or a hyperbaric chamber may be considered for valuable animals. Because the disease may recur, affected animals should not be returned to high altitudes.

Affected cattle should not be retained for breeding because of heritability. Treatment of concurrent diseases, including respiratory/cardiac disease, GI disease, parasitism, and plant toxicosis, should be addressed. Because locoweed poisoning has been directly linked to the development of CHF in cattle, the exposure of susceptible animals to locoweed should be minimized by ensuring that animals have a good selection of forages. Animals should be moved to pastures free of locoweed as soon as poisoning is recognized to prevent severe and irreversible damage.

Treatment of BHMD can be expensive and unrewarding, so prevention is preferred. Genetic selection through the use of pulmonary arterial pressure (PAP) measurements to select cattle resistant to the effects of hypoxia is a more effective way to control BHMD. Identifying animals highly susceptible to the effects of altitude hypoxia (those with high PAP measurements) and eliminating them from the breeding pool are practical methods to reduce the prevalence of BHMD in a herd. The PAP measurement procedure involves passing flexible polyethylene catheter tubing (1.19 mm internal diameter × 1.7 mm external diameter) through a large-bore needle (12 or 13 gauge, 3.5 in.) inserted into the jugular vein. The catheter is advanced through the jugular vein to the right atrium, into the right ventricle, and then into the pulmonary artery.

At altitudes of 5,000–7,000 ft (1,524–2,133 m), a normal mean PAP measurement should be 34–41 mmHg. In cattle displaying signs of pulmonary artery hypertension, the PAP can range from 48–213 mmHg. The PAP and the RV pressure may be normal to subnormal in cattle with end-stage right CHF because of the failing myocardium. Cattle with ventricular septal or atrial septal defects often have mean systolic and diastolic measurements in the hundreds. Any animal with a PAP measurement >48 mmHg is considered at risk of developing BHMD and may be a potential genetic carrier and should not be maintained or used in breeding programs at high altitude. These animals should also be auscultated for cardiac murmurs and evaluated for possible congenital cardiac defects. In general, cattle >1 yr old that have a PAP <41 mmHg at an elevation >5,000 feet (1,524 m) are likely to maintain an acceptable PAP at high altitude and serve as good breeding stock for herds at high elevation. PAP measurements between 41 and 49 mmHg are difficult to interpret consistently; these animals should be used with caution at high elevation.

Multiple factors contribute to the variation of PAP in cattle, including breed, gender, age, body condition, concurrent illness, environmental conditions, elevation, and genetics. Based on tests of >300,000 head of cattle, it appears that no one breed is resistant to the effects of high-altitude hypoxia, although some breeds, and pedigrees within breeds, appear to be more naturally resistant. It is not unusual to see a difference in PAP measurements between heifers and bulls because of
husbandry practices. Bulls are often pushed nutritionally for faster growth and muscling, which may affect pulmonary function and give rise to pulmonary hypertension. Pregnant cattle have been noted to have a higher PAP measurement than nonpregnant cattle. The age of the animal at the time of PAP testing should always be considered, because there is greater variation and less predictability in cattle ≤1 yr old. Testing animals at ≥16 mo of age appears to be the most consistent and accurate at predicting susceptibility to pulmonary hypertension induced by high altitude. Any concurrent illness, especially respiratory disease, or any cause of temporary or permanent pulmonary hypoxia can influence the PAP measurement.

Some cattle appear to be prone to developing right CHF, whereas others live at high altitude with a documented increased PAP and never have a clinical problem. Even though these animals may not develop clinical BHMD, they can pass the genetic predisposition to their offspring. This variable expression of clinical disease and the variable penetrance of the gene makes PAP testing challenging at all elevations and becomes an even greater concern at elevations <5,000 ft (1,524 m) where the hypoxic conditions needed to stimulate a pulmonary response are not sufficient. PAP measurements taken at low elevations (<5,000 ft [1,524 m]) should not be used as a positive selection tool but only to identify animals highly susceptible to hypoxic conditions and hypertensive even at elevations <5,000 ft (1,524 m). Cattle moved from low elevations to high elevations should remain at the altitude for ≥3 wk before PAP testing.

Future advancements in the research of pulmonary hypertension in cattle are concentrating on identifying DNA markers for recognition of genetic carriers of pulmonary hyperresponders to hypoxic conditions. Other areas of interest and research are being directed at and addressing the alarming increase in incidence of RV CHF at lower elevations as seen in heavy feedlot cattle at elevations ≤4,000 ft (1,219 m). These fat cattle at this elevation seem to have the same postmortem lesions as those seen at higher elevations.