

## **HIGH ALTITUDE DISEASE, PAP, FEEDLOT HYPERTENSION, AND RESPIRATORY ISSUES**

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### **IMPLICATIONS**

Right-heart failure (RHF) due to pulmonary hypertension, more commonly known as brisket disease or high altitude disease, is a complex disease that is becomingly increasing problematic for the cattle industry—regardless of altitude. The disease became known as high altitude disease because until the mid-1960s RHF was only reported at altitudes over 7,000 ft. Today, RHF is still problematic in high altitude cow-calf operations and is occurring with increasing incidence in feedlot cattle. The clinical signs are commonly mistaken for chronic pneumonia, which complicates disease diagnosis and reporting. Moreover, cattle treated for pneumonia have 2 to 3 times greater risk of developing RHF than cattle not treated. An ongoing investigation of beef cattle mortality on a feedlot at 3,000 ft. in the Texas Panhandle indicates that respiratory disease and RHF are intimately linked. Cattle with evidence of pneumonia may have actually died from RHF; however, close examination of the heart is required for an accurate diagnosis.

### **INTRODUCTION**

One hundred years ago, two researchers from the Colorado Agricultural College, now Colorado State University, set out to investigate a strange new disease that was killing cattle in South Park, Colorado. These researchers, George Glover and Isaac Newsom, gave this new disease the name brisket disease because one of the clinical signs included swelling of the brisket (Glover and Newsom 1915). They concluded that the disease was caused by exhaustion of the heart due to the low oxygen levels associated with high altitude exposure. The progeny of bulls originating from low-altitude were reported to be particularly susceptible to PAH, providing the first evidence for a genetic basis to the disease (Glover and Newsom 1915). The disease also became known as ‘high altitude disease’ because, up until the 1960’s, the disease was only seen at altitudes over 7,000 ft. (Hecht et al. 1962).

Studies of the bovine lungs and pulmonary arteries, conducted in the early 1960s, revealed that a key process in the development of pulmonary hypertension was the remodeling of the pulmonary arteries (Alexander and Jensen 1963a; b). In the same year, however, it was also reported that cattle with RHF have increased resistance to blood flow downstream of the pulmonary capillaries (Kuida et al. 1963). The increased

resistance suggests that narrowing and remodeling of the pulmonary veins, which return the oxygenated blood to the left side of the heart, may also contribute to the development of pulmonary hypertension. This latter finding remains to be investigated.

Differences between right heart failure (brisket disease) and other causes of heart failure

Brisket disease or RHF should not be confused with other causes of heart failure. These other causes affect specific areas of the heart:

1. Pericarditis: inflammation of the pericardium, the outside of the heart. Hardware disease (traumatic pericarditis) is a common example
2. Myocarditis: inflammation of the myocardium, the wall of the heart. *Haemophilus somni* infection of the left ventricle is one example
3. Endocarditis: inflammation of the endocardium, the inside lining of the heart. Bacterial colonization of the major heart valves is one example.

Brisket disease differs from the above heart diseases because, unlike the above, the disease does not involve a specific area of the heart. Rather, the entire right-heart is involved due to narrowing of downstream vessels, in the pulmonary arteries—this is technically called cor pulmonale. Importantly, on necropsy examination, the above diseases can produce similar lesions to RHF; consequently, the heart must be closely examined for other possible causes of heart failure.

Low oxygen levels in the lung cause right-heart failure (brisket disease)

So why do the pulmonary arteries begin to narrow and restrict flow? For 3 possible reasons: 1) High altitude exposure, 2) Diseases of the lung such as pneumonia, and 3) Slow or shallow breathing. All 3 factors can trigger the disease through one common mechanism: they reduce the amount of oxygen entering into the lung. The low levels of oxygen cause the pulmonary arteries to contract and narrow; this increases the resistance to blood flow—just like a blocked irrigation pipe—and causes the blood pressure in the pulmonary arteries to rise. This is why cattle that have a high pulmonary arterial pressure (PAP)—greater than 49 mm Hg—are thought to be at greatest risk of brisket disease (Holt and Callan 2007).

Incidence of right-heart failure (brisket disease)

Unfortunately, we do not have a reliable estimate of the RHF incidence in the cow-calf industry. One study, from 50 years ago, estimated the annual incidence of RHF to be ~1% of all cattle at altitudes over 7,000 ft. (Hecht et al. 1962). The true incidence, however, is likely to be even greater given that the clinical signs of RHF are often mistaken for respiratory disease (Glover and Newsom 1915; Malherbe et al. 2012; Neary et al. 2013). Furthermore, despite current mitigation practices, RHF is still problematic for high altitude cow-calf producers (Neary et al. 2013). On one cow-calf operation at an altitude of > 8,000 ft., RHF was responsible for half of all calf death loss between branding in the spring and weaning in the fall (Neary et al. 2013).

We have more reliable estimates of RHF incidence in the feedlot industry. In a recent epidemiological study, which involved 1.6 million cattle fed in 15 feedlots across North America, we found that the incidence of RHF doubled from the years 2000 to 2008

(Neary et al. 2015a). In 2012, 15 out of every 10,000 cattle entering US feedlots died of RHF (Neary et al. 2015a). A study, conducted in the mid-1970s, of 4 U.S. feedlots located at an altitude of 5,000 ft. reported the risk of CHF to be 3 cases per 10,000 cattle entering the feedlot (Jensen et al. 1976). Although direct comparisons between these two studies cannot be made, the findings do, however, suggest that the incidence of RHF has increased in the feedlot industry. Furthermore, RHF was observed in feedlots at all altitudes (Figure 1); consequently, ‘high altitude disease’ may not be an appropriate name for RHF, at least in feedlot cattle—high altitude merely increases the baseline risk.

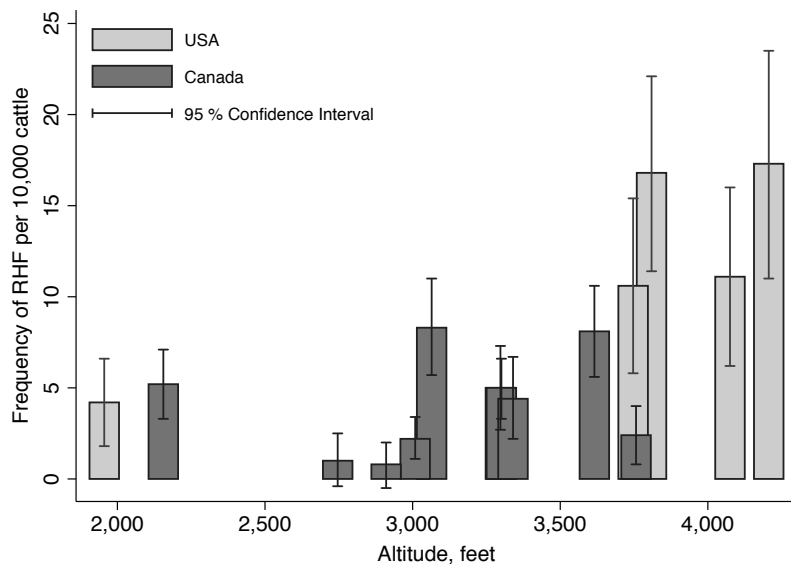


Figure 1. The risk of right-sided congestive heart failure (RHF) or brisket disease in Canadian and U.S. feedlots in 2012 according to feedlot altitude. The risk of RHF appears to be greater in feedlots located at higher altitudes.

In another study, involving 152 Angus steers, we found that mean PAP increased with age from calfhood to the late feedlot finishing phase (Neary et al. 2015b). Mean PAP increased from 4-months ( $39 \pm 3$  mm Hg; mean  $\pm$  SE) to 6-months of age ( $42 \pm 3$  mm Hg) at an altitude of 7,200 ft., and from 13-months ( $43 \pm 1$  mm Hg) to 18-months of age ( $50 \pm 1$  mm Hg) at an altitude of 4,000 ft. These findings indicate that PAP may actually be greater in the feeding period at low altitude than in suckling calves located at higher altitudes. Furthermore, the increase in mean PAP through the feeding period may explain why RHF typically occurs around 4-months on feed (Neary et al. 2015a).

### Clinical signs

In many cases, brisket disease occurs undetected because the clinical signs of congestive heart failure are variable and may be confused with respiratory disease (Glover and Newsom 1915; Malherbe et al. 2012; Neary et al. 2013). These include labored, or open-mouth, breathing, rough hair coat, glazed eyes, and reluctance to move. More specific signs of heart failure include swellings of various body regions including the brisket region (hence, brisket disease), belly, and under the jaw. The jugular vein will also become engorged with blood and, later in the disease, may show pulsations, which indicates that the major valve in the heart (tricuspid valve) is leaking.

## Necropsy findings

On necropsy examination, cattle that died of RHF will have an enlarged, flabby right ventricle (the chamber of the heart closest to the head) (Figure 2). Other findings typically include,

1. Enlargement of the liver and a mottled or 'nutmeg' appearance when sliced,
2. Fluid accumulation in the chest and abdomen,
3. Edema (fluid accumulation) of the intestines and mesentery (membranous tissue in the abdomen),
4. Enlargement of the mesenteric lymph nodes (due to edema)
5. Fluid accumulation in the pericardial sac (membrane surrounding the heart).

Other potential causes of heart failure—previously described—must also be ruled out.

Unfortunately, there is no treatment for this disease and many of the risk factors remain unknown. This is concerning for the cattle industry, particularly if the incidence of the disease continues to climb.

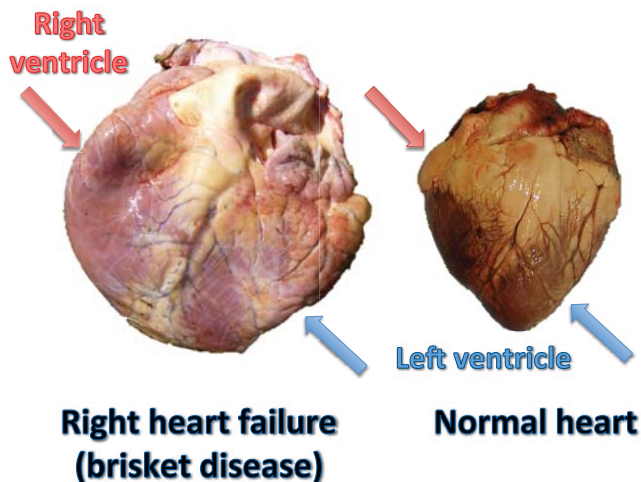


Figure 2. Narrowing of the pulmonary arteries in response to low levels of oxygen in the lung increases resistance to blood flow pumped through the lung by the right ventricle or chamber of the heart (top left arrows). The increased workload causes the muscular wall of the right ventricle to thicken in order to match the increased vascular resistance. Chronic pressure overload eventually causes the pumping capacity of the myocardium to decline, and the right ventricle to enlarge owing to incomplete filling and emptying during the cardiac cycle. Eventually, the heart can no longer function to pump blood through the pulmonary circulation – the valves begin to leak and contractions are further impaired as cardiac muscle cells die and are replaced with fibrotic lesions – leading to heart failure and death. The left ventricle (bottom right arrows) always forms the apex of the heart, the lowest part of the heart as it sits in the chest, and is closer to the diaphragm than the right ventricle.

## PULMONARY ARTERIAL PRESSURE (PAP) MEASUREMENT

Unfortunately, we cannot directly determine an animal's risk of RHF. Instead, we have to rely on pulmonary arterial pressure (PAP) measurement (Holt and Callan 2007); the greater the mean PAP, the greater the supposed risk of RHF. Cattle with a mean PAP greater than 49 mmHg are considered to be at particularly high risk and should be moved to a lower elevation to avoid the onset of RHF. Since mean PAP is moderately to

highly heritable (Shirley et al. 2008), it is reasonable to assume that we might be able to reduce the incidence of RHF among a calf crop by only breeding cattle with 'low' PAP measurements. To be accurate, PAP measures must be obtained at the altitude (or higher) at which the cattle are to be pastured.

PAP measurements performed at a lower elevation than the altitude at which the cattle are to inhabit provide little information: a low PAP measurement does not mean that it will also be low at a higher elevation; however, an individual with a high PAP measurement at low altitude should not be taken to higher altitude because it is already a high-risk candidate for RHF. PAP measurement has been largely successful at reducing the incidence of RHF among cattle located in the high country; however, because the technique requires specialist equipment and veterinary expertise, its application has been largely limited to the paternal line. It should also be noted that most PAP measures are collected from yearling bulls and replacement heifers. Therefore, additional research is needed to understand what these yearling measures infer to pre-weaning calves, and conversely, finishing steers.

Recently a variant of the gene encoding Hypoxia-Inducible Factor-2 (EPAS1) was discovered that predicts, in part, the tendency of beef cattle to develop elevated PAP when exposed to high altitude, raising the possibility that genetic testing may provide solutions for improving cattle breeding practices and reducing the risk of pulmonary hypertension and right heart failure (Newman et al. 2015).

## **RESPIRATORY ISSUES**

Unfortunately, the clinical signs of RHF are similar to those of respiratory disease (Glover and Newsom 1915; Malherbe et al. 2012; Neary et al. 2013); consequently, many cases of RHF are likely misdiagnosed and mistreated. Further, calves with RHF may also have concurrent, or residual scarring from, respiratory disease (Neary et al. 2013). We have previously found that feedlot cattle treated for respiratory disease are 2 to 3 times more likely to develop RHF than cattle not treated for respiratory disease (Neary et al. 2015a). In an ongoing investigation into cattle mortality at one feedlot located at 3,000 ft. in the Texas Panhandle, we have identified that lesions of the pulmonary arteries and right ventricle are commonly associated with pneumonia. Furthermore, in many cases it appears that pneumonia was responsible for the development of RHF but it was RHF that was the cause of death. This raises many questions: Are necropsies commonly misdiagnosed as respiratory disease when in fact the animal died of RHF? Does pulmonary hypertension predispose cattle to respiratory disease, as well as RHF? Could pulmonary hypertension reduce the effectiveness of antimicrobials for treatment of respiratory disease?

## **LITERATURE CITED**

Alexander, A. F., and R. Jensen. 1963a. Pulmonary arteriographic studies of bovine high mountain disease *Am. J. Vet. Res.* 24: 1094-1097.

Alexander, A. F., and R. Jensen. 1963b. Pulmonary vascular pathology of high altitude induced pulmonary hypertension in cattle. *Am. J. Vet. Res.* 24: 1112-1122.

