NEW THOUGHTS ON BOVINE PULMONARY HYPERTENSION

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We've been breeding oxygen hungry cattle for the past 50 years. The bovine pulmonary system is undersized and overworked. We are now at the point where the bovine cardiopulmonary system is working at nearly maximum capacity even at rest in growing cattle. Stressed systems are prone to failure. In order to reduce mortality from BRD and pulmonary hypertension cattle need to acquire and utilize oxygen more efficiently.

The Old Story of Brisket Disease and Bovine Respiratory Physiology

One hundred years ago in South Park, Colorado the effects of hypoxia on cattle became apparent when a curious disease was investigated by two CSU researchers, Glover and Newsom, in response to requests from two producers, Lew Robbins and David Collard. The problem was known as brisket disease or high-altitude disease because it affected cattle at high altitudes and led to fluid accumulation in the tissues under the chest, eventually leading to death. The researchers did clinical investigations, explored the epidemiology, performed pathologic and physiologic investigations, and ultimately did breeding trials to establish the genetic basis of susceptibility to this disease.

Cattle at high altitudes (>6,000 ft) are exposed to low oxygen tension in the air they breathe. Alveolar hypoxia induces a response of the small pulmonary arterioles, first causing muscular contraction that limits flow, followed by remodeling of the arteriolar tissues after more chronic exposure. This response is more pronounced in cattle than other species, and in some strains of cattle the response is exuberant. In cattle with lung damage this response helps redirect blood to other parts of the lung. In cattle with low oxygen throughout the entire lung it causes severe increases in pulmonary artery pressure. With chronicity this obliges the right side of the heart to pump against abnormally high pressure, ultimately leading to heart failure. The classic signs of brisket disease are the signs of right-sided congestive heart failure. The predisposing cause is pulmonary hypertension induced by alveolar hypoxia.

A test was developed to measure pulmonary artery pressure (PAP) in the field. Using this test cattle with exuberant pulmonary artery pressor response can be identified and excluded from breeding. Breeds of cattle that were developed in lowlands, such as Angus and Hereford, had not had selection pressure that prepares them for high-altitude environments, and many such cattle respond poorly to low oxygen. By selecting breeding bulls that have low PAP, after several generations the problem of high-altitude disease was expected to become history. By the 1980s veterinarians were providing PAP testing services, and many ranchers were using PAP testing results.

But the problem of bovine pulmonary arterial hypertension (PAH) did not go away. As long ago as the 1960s it was recognized that some cattle in feedlots developed the same evidence of right-sided congestive heart failure near the end of the feeding period. Since it was not associated with high-altitude disease it became known as 'fat steer disease'. It was noted to occur in the most rapidly growing animals on full feed, and it occurred in feedlots below 5000 feet altitude.

High mountain ranchers, even after instituting PAP testing and bull selection over 2 to 3 decades still see higher death losses in their pre-weaned calves than their lowland counterparts. While they see few cases of classical brisket disease, some of their fastest-growing calves develop severe respiratory problems and die unless they are brought to low altitude promptly.
Revisiting an old problem

The Integrated Livestock Management (ILM) Program was developed at CSU in 1996 to provide creative solutions for the challenges that face the livestock industries through research, information delivery, and postgraduate training. High mountain ranchers facing significant calf loss approached our group to ask for help.

Drs. Tim Holt, Frank Garry, and Joe Neary in the Department of Clinical Sciences at the College of Veterinary Medicine and Biomedical Sciences approached the problem as a clinical and epidemiological investigation, much like Glover and Newsom 100 years before. Survey results of Colorado producers demonstrated clearly that high-altitude cattle suffer much higher levels of respiratory disease and death loss. Surveyed producers described few cases of brisket disease but defined a problem they called “summer pneumonia”. No previous scientific investigations of this phenomenon had been done because of the inaccessibility of cattle summered in the mountains. Dr. Neary spent the summer riding the range, sampling affected animals, and performing postmortem examination of dead calves. Some calves died from bronchopneumonia, and others from pulmonary hypertension. The histopathological lesions found from tissue samples demonstrated pulmonary arterial hypertension and chronic damage and change to the pulmonary arteries, but with a different distribution and character of pathologic changes distinct from those produced by alveolar hypoxia.

In 2010, calves located at altitudes over 2,731 m (8,960 ft.) on one ranch in south-west Colorado were extensively monitored from horseback 6 days per week from July 10th to October 5th. In total, 612 calves were turned out with their dams onto summer grazing. Of those 59 (9.6%) were either known to have died or were presumed to have died by the time of weaning. Ante-mortem clinical signs of BPH and BRD showed many similarities making disease diagnosis difficult. Clinical signs can resemble respiratory disease even in the absence of underlying pneumonia. In total, 23 necropsies were performed on this ranch. Of those, 12 died from lesions consistent with bovine respiratory disease (BRD) and 13 died from lesions consistent with bovine pulmonary hypertension (BPH). This study raised 2 important questions. Firstly, are calves located on ranches at higher altitude at a greater risk of developing BRD? Secondly, are calves dying from BPH in a herd that has only bred bulls with low pulmonary arterial pressures (PAP) (< 42 mmHg) for over 20 years?

In order to answer the first question a survey was sent out to Colorado Cattlemen’s Association members in the summer of 2010 assessing calf health and mortality between turnout onto summer grazing and weaning in the fall. It was found that an increase in the altitude at which pre-weaned beef calves were located on August 1st was a significant risk factor for a below average herd weaning percentage. That is the proportion of calves turned out onto summer pastures that were subsequently weaned. The latter association was due to the increased incidence of diseases involving the cardiopulmonary system with increasing altitude such as BPH, or high altitude disease, and summer pneumonia (Fig. 1). This suggests that the calf death loss from BRD on the high altitude ranch studied was likely to be greater than a similar ranch located at lower altitude. Calves do not reach optimal pulmonary function until at least one year of age.10 This means that they are particularly susceptible to the potential effects of low oxygen environments.
Figure 1. The mean herd prevalence of disease syndromes by the altitude at which calves were located on August 1st

BPH, known descriptively as "brisket disease" and "high altitude disease" was first reported to occur one century ago at altitudes over 7,000 ft. in Colorado. It was later determined that, in response to chronic alveolar hypoxia associated with high altitude, vasomotor tone initiates, and the high ensuing intravascular pressures advances, medial hypertrophy of the small pulmonary arteries. Studies suggest the pulmonary pressor response to be moderately heritable. This means that managers of high altitude herds that select sires with low pulmonary arterial pressures, typically ≤ 45 mmHg, should be able to reduce the incidence of high altitude disease within their herds. However, it may be the BPH is much more complex than we originally believed.

Work at lower altitudes

These investigators extended their studies to healthy calves at varying altitudes. Recently developed technology allows field measurement of blood gases. From these measurements we can estimate oxygen supply, demand, and consumption by tissues. Calf pulmonary physiology had been well studied in laboratories over 30 years ago at altitudes approximating sea level. At that time calves were smaller and had a slower growth rate. There have been few studies to characterize calves at 5000 feet. Studies above 5000 feet have been performed on individual animals in hypobaric chambers for short periods of time. Because of technology limits there have been no studies of populations in the field with chronic exposure to altitudes of 5000 feet and above.

Findings from these field studies were startling. Calves from herds at 9000 feet are consistently starved for oxygen. Very low levels of blood carbon dioxide demonstrate that apparently healthy calves are breathing at a maximal level. Despite their efforts, blood oxygen levels were only half of expected levels at low altitude. Average arterial oxygen tension in calves at 1, 3 and 6 months of age were 50 mmHg and below, while reference levels for calves at low altitude range between 87 and 106 mmHg. Blood lactate levels were 2 to 3 times expected levels at low altitude demonstrating a significant degree of anaerobic metabolism. Other blood biochemical changes demonstrated low levels of damage to the kidneys, which are organs that are highly oxygen dependent.

Even more remarkable were our findings from apparently healthy calves at 5000 and 7000 feet. It would seem reasonable to assume that calves at 9000 feet are living in a high stress environment. Calves at lower altitudes, however, showed similar patterns with only slight improvement in their blood gas values. Even at 5000 feet
calves were consistently hyperventilating to improve their oxygen supply, but still able to maintain oxygen tension at only 60 mmHg. These results demonstrate that calves have little cardiopulmonary reserve. Even at rest their heart and lungs are working near maximal capacity. Furthermore, even in herds where the breeding program has selected against cattle with exuberant pulmonary artery response to hypoxia, PAP testing shows high levels of pulmonary hypertension. Even with oxygen supplementation these levels diminish only marginally, suggesting that inhaled oxygen alone does not reverse the trend of pulmonary arterial response.

**How to make sense of these findings**

In the 1970s anatomy researchers compared cardiopulmonary capacity of various animal species. Their findings demonstrated that cattle of that time had very limited cardiopulmonary reserve. For example cattle use about two times as much oxygen as horses for their metabolic demands, but have about 30% as much total lung volume. Both species would do okay standing, eating and growing. But the horse has a tremendous amount of reserve that it can use when it needs to run. Even in the 1970s cattle had very little cardiopulmonary reserve. The investigators noted that this left cattle uniquely susceptible to infectious respiratory diseases and other cardiorespiratory problems whenever they faced stresses that increased demand.

On the other end of the research spectrum human medical researchers pursued the causes and manifestations of pulmonary hypertension. PAH is a remarkably common human health problem that occurs both as a primary disease entity and as a manifestation of multiple other disease problems. In the humans alveolar hypoxia does produce PAH as in cattle, but it is only one of five different groups of pulmonary hypertension mechanisms. The understanding of primary hypertension has undergone a paradigm shift in the last decade. As with cattle the condition was once considered to be primarily a manifestation of altered arterial constrictor tone, but is now seen as a vascular disease driven by numerous different cellular and inflammatory mechanisms.

it seems that BPH is much more complex than we originally believed. In humans, alveolar hypoxia is just one of 5 disease pathways to chronic pulmonary hypertension. Similar to the syndrome in human beings, multiple, but not mutually exclusive, subcategories of bovine pulmonary hypertension may exist. This may explain the apparent change in the clinical signs associated with pulmonary hypertension over the years from the classic, rapid-onset condition producing “belly-draggers” to a slower more insidious-onset pulmonary hypertension associated with vague clinical signs that share similarities with pneumonia. This would explain the persistence of pulmonary hypertension in high-altitude herds that have bred only bulls with low PAP and its occurrence at lower altitudes. A similar pattern of events has occurred in the broiler industry. A broiler's risk of developing pulmonary hypertension is proportional to its oxygen demand or metabolic rate. It is thought that broilers have inadequate pulmonary vascular capacity to accommodate the high cardiac output necessary to meet the metabolic demand of fast growth. The disease was initially reported at high altitude but continued selection for rapid growth along with the short generation time of chickens meant that it wasn’t long before the disease was reported to occur at sea level.15 Similarly, a calf's PAP is positively correlated with growth rate. Preliminary data from our ongoing studies suggests that cardiopulmonary insufficiency may be a risk factor for BPH.

Over the last several decades cattle producers have worked hard to improve the genetics of their cattle with a focus on enhanced growth rate, muscling, and body composition. With the exception of producers who preselected bulls for their resistance to exuberant arteriolar response to alveolar hypoxia, almost no selection pressure has been applied to improving cardiopulmonary performance. PAH in cattle can result from alveolar hypoxia as is seen in high-altitude animals that develop brisket disease. But PAH can also develop in cattle from a variety of other mechanisms despite previous selection for resistance alveolar hypoxia.

Our findings from calves at 5000 feet altitude and higher suggest that oxygen demand of fast-growing beef calves has begun to exceed the ability of the cardiopulmonary system to supply oxygen. These calves are working hard to breathe and still maintaining circulating oxygen tension at marginally acceptable levels. In the face of any kind of stress including high growth rate, co-mingling, exercise, or high-altitude such calves can easily exceed their limited cardiopulmonary reserve making them more susceptible to cardiorespiratory disease. Most feedlot cattle in the United States reside between four and 5000 feet altitude. Despite advances in the development of new vaccines, antibiotics, feeding regimens, and cattle management techniques respiratory disease remains the number one cause of feedlot cattle disease and death. Almost all research on bovine respiratory disease complex has been focused for several decades on the infectious agents, animal response to infection and pharmaceuticals to modulate the disease. In the last 30 years virtually no one has asked questions...
about the underlying cardiopulmonary physiology of these animals. Recent anecdotal reports from feedlots identify an increasing rate of occurrence of fat steer disease, the lowland equivalent of brisket disease in fattening cattle.

Our overarching hypothesis is that oxygen supply and demand is imbalanced in the rapidly growing beef calf. This hypothesis is supported by previous physiological studies, improved understanding of the phenomenon of PAH, high morbidity and mortality rates in high-altitude cattle, and the occurrence of PAH with different manifestations than those occurring from alveolar hypoxia alone.

**Further observations**

We have continued to study beef calves at varying altitudes. In addition to measuring PAP we have analyzed both arterial and venous blood gases, muscle growth and frame size. We have identified a strong correlation between alveolar – arterial oxygen gradient and ribeye area suggesting that calves with greater ability to take up oxygen and transport it to the tissues can remain healthy and perform better. On the other hand increased growth rate is strongly associated with increasing PAP suggesting that increased demands on the cardiovascular system are strongly associated with increasing vascular change in the lungs.

By measuring both venous and arterial oxygen tensions we have begun to evaluate total oxygen consumption in response to demand. In rapidly growing cattle the oxygen extraction greatly exceeds normal values for the species suggesting that they need to utilize virtually as much oxygen as the cardiopulmonary system can supply. There are clear associations between oxygen extraction and elevated PAP levels.

We are currently evaluating calves at various altitudes from nursing through finishing in feedlots. We are studying the relationships between cardiopulmonary function, growth, and altitude, and performance in feedlots from arrival through finishing, including health and performance. The studied calves will be followed to slaughter so that we can also evaluate the relationships between PAP, pulmonary function and the occurrence of lung and pulmonary artery lesions at harvest.