

It's Not Just a High-altitude Disease

Researchers are finding genetic component for pulmonary artery hypertension.

by Heather Smith Thomas

For many years, cattle producers have noticed that some cattle at high elevations suffer pulmonary artery hypertension, which leads to congestive heart failure. What many producers don't realize, however, is that this condition can also affect cattle at lower elevations, especially feedlot animals near finish weight, and that there may be a genetic component.

This condition has been called by many names, including brisket disease, big brisket, mountain sickness or high-mountain disease. Affected animals are usually lethargic and develop edema (swelling) in the neck and brisket due to

high blood pressure forcing fluid out of the vessels into surrounding tissues. Swelling may spread up the neck or under the belly. Unless the condition is reversed, the animal dies. Sometimes you don't see outward signs; you just find the animal dead from heart failure.

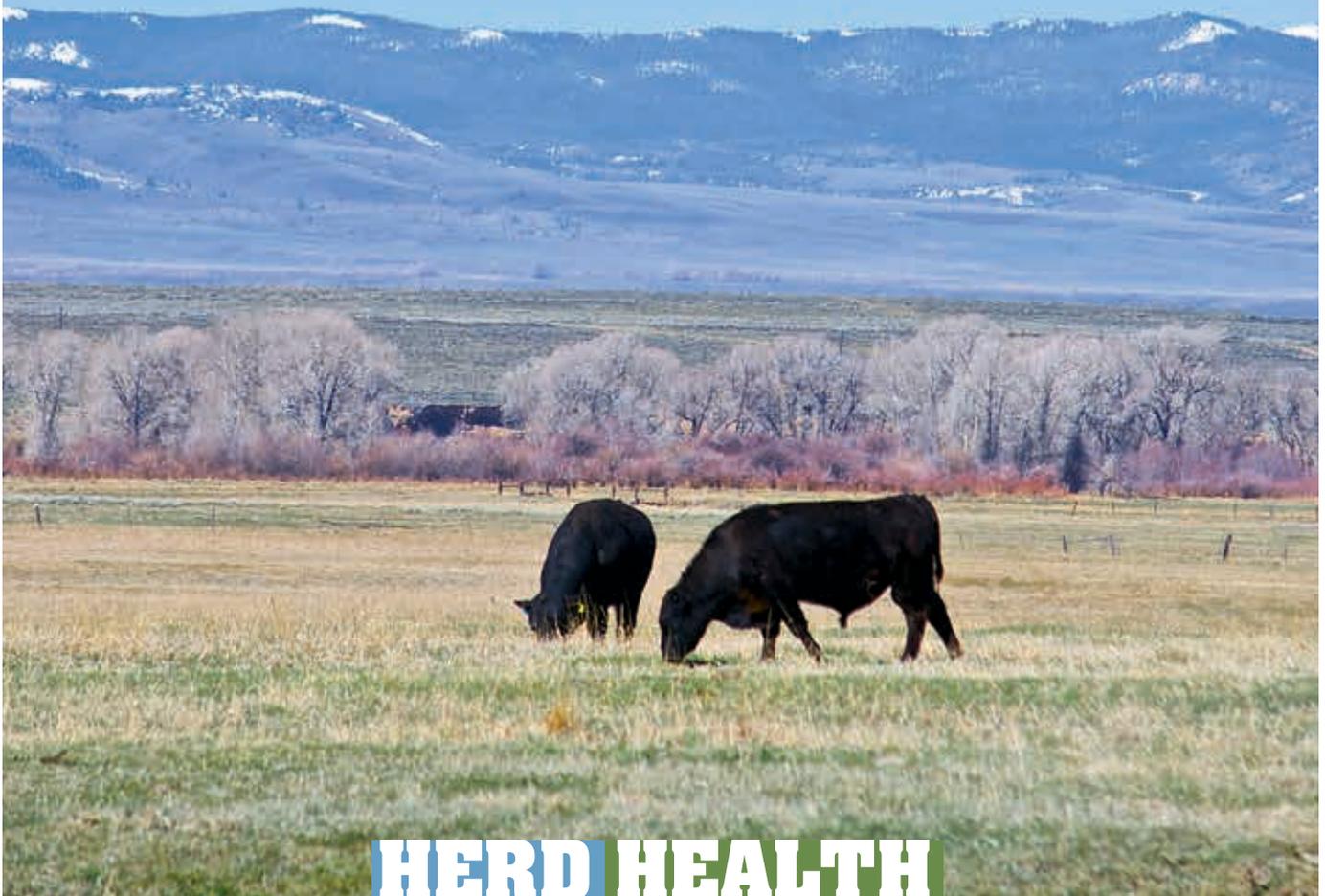
Susceptible cattle living at elevations above 5,000 feet (ft.) are at risk, and incidence of brisket disease increases at higher elevations. In the thinner air of high elevations, low oxygen availability triggers the problem. Susceptibility seems to be inherited. Affected animals often have problems early in life if they live at a high elevation, or develop the problem if

brought to high elevation from lower altitudes.

Tim Holt, veterinarian with Colorado State University (CSU), has been studying brisket disease for more than 35 years and has tested cattle at elevations from sea level to 15,000 ft. He uses a test developed in humans for measuring pulmonary arterial pressure (PAP). The PAP test determines which animals are most at risk for brisket disease.

He says the low level of oxygen in the air at high elevations causes the inside diameters of arteries in the lungs to contract. The muscle layer in the artery wall

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thickens, reducing blood flow into and through the lungs and increasing blood pressure. The smaller the diameter of the vessel, the greater the pressure.

The extra effort needed to pump blood causes enlargement of the right side of the heart. Eventually, the right ventricle loses its ability to contract. As blood pressure increases and starts to back up into the heart, it can blow out the valves of the right ventricle.

Measuring the pressure

The PAP test measures that pressure. There are several reasons why an animal may develop this problem, but Holt says a big reason could be genetic susceptibility. The PAP test measures pressure in the lung and blood-flow resistance, making it possible to predict an animal's welfare at high altitudes. To be accurate, the test needs to be performed at elevations above 6,000 ft.

The problem sometimes appears in feedlot cattle, even at low elevations, as they get heavier and closer to finishing weight because the heart must work harder. They often die of right heart disease.

Research is currently being conducted in feedlot cattle at lower elevation, because these cattle can have the same clinical appearance. Greta Krafus, a veterinarian and doctoral student in the CSU Department of Microbiology, Immunology and Pathology, is studying the heart and lungs of these fat cattle. It is a challenge to

► **Below:** "The key word here is polygenic. It's not just one gene; it's whole-animal physiology," says Milt Thomas.

unravel the condition and possible causes, such as hypoxia, metabolic overload and bovine respiratory disease (BRD).

Milt Thomas, also with CSU, is part of a team of researchers looking at genetic factors and genomics.

"It can be a problem any time you put cattle above 6,000 feet, yet there are examples of herds that exist at high altitudes that have never had a problem," he says. "There are also examples where someone moved cattle from low elevation to high elevation and had a high percentage of cattle affected. It is extremely variable, and we've known for at least 50 years that there is a genetic component. That knowledge helped us develop what we call an indicator trait, the measurement of pulmonary arterial pressure."

The PAP test is a physiological measurement, Thomas says. In humans, the measure is called PA pressure and is used to determine the condition of the interaction between a person's heart and lungs. A high PAP test (taken to ascertain if the animal is tolerating high altitude) is one use of this tool, but he says there are a variety of things that can result in a high PAP score.

Thomas says the challenge of dealing with brisket disease is that it generally occurs late in life, not in a young calf, so by the time producers see signs of the disease, it is too late to save the animal. To help with early detection, veterinarians use the PAP test as an indicator.

"It's a great veterinary tool, and Tim Holt and his group have been training other veterinarians to work with this, but we have to understand that it is simply a physiologic

indicator," he explains. It is like checking a patient that already has a problem, and it also is just a measure of a symptom, not a diagnosis of a specific disease.

"A similar example of a physiological indicator that we use in humans is blood pressure," he continues. "There are many, many things that can make blood pressure go up. In some people, it's high altitude." Stress of nearly any kind might cause a person's blood pressure to rise.

Thomas says there is still much to be learned about pulmonary hypertension. Even though producers and veterinarians have been aware of brisket disease for 100 years, he says it is still a challenging problem.

"This condition probably always will be, even if we find a solution, because people will still breed cattle that have these types of problems," Thomas says.

Producers like to breed to prominent artificial insemination (AI) sires. Those sires may work fine at low elevation, but we don't know what their progeny will do at higher elevation. Some may have problems that the producer is not aware of until after the calves are born.

Genetic improvement and genomics

When the term "genetic improvement" is used from a beef cattle standpoint, Thomas says, we tend to think about characteristics like improvement in growth rate, more pounds of beef, better marbling scores and carcass quality.

Expected progeny differences (EPDs) are the best tool for that type of selection, he explains, but if a person is selecting for growth, it is often easier to pick the bigger bulls and bigger heifers and mate them to each other.

There is always a tradeoff. When selecting for growth and feedlot performance, producers may lose maternal traits and other desirable qualities. There is no free lunch; when you select for one thing, you may affect another trait antagonistically. Keeping a balance is always the challenge.

"Our group here at CSU has been developing and perfecting a PAP EPD that can be used in selection to avoid brisket





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disease, and has worked on this for nearly 30 years. The general success of an EPD usually boils down to whether the trait selected is high or low in heritability. In this case, most of our evidence suggests that PAP as the indicator trait of tolerance to high altitude is at least moderately heritable and in some cases highly heritable. Therefore we are saying there is a genetic component,” says Thomas.

Thomas says Mark Enns and Scott Speidel have worked on the genetic component, trying to develop a better PAP EPD. He notes there is now a collaboration with the American Angus Association to pool resources to accomplish this.

“We have entered into the world of genomics, so we are now using genomic information within the EPD system,” he says. “When we first started getting genetic markers, people thought we’d no longer have to collect all the data for this challenging EPD system, but that hasn’t proven true. We have actually used a multi-trait system where we use genomic information within the current EPDs.”

One example of this type of use is ribeye area. Thomas says most breed associations that measure ribeye area use multiple sources of data, including carcass data from a packing plant, ultrasound measures and animal size.

“If you are measuring yearling bulls for ribeye area EPD, you would weigh them,

and there is probably a strong correlation in that bigger bulls have bigger ribeye areas,” he says. “Therefore, we develop a multi-trait model, and if we also have genomic information for ribeye area we can put that into the model. This makes it a very robust multi-trait EPD.”

Thomas and his team have been studying all the correlated traits between growth and PAP, and related traits. In some data sets, he says there have been some very strong correlations observed between growth rate and PAP scores, but it is not true in every data set.

Thomas began his career with CSU as the John Rouse Chair, working with the Rouse Ranch, the One-bar Eleven, and the Colorado Beef Improvement Center in Saratoga, Wyo.

The Rouse Ranch has about 420 Angus mother cows raised on this ranch since the 1950s, and Thomas says he has an extensive data set with those cattle.

“Currently, we have records on about 12,000 animals, and 6,000 of them have PAP scores,” he explains. “We also have high-density genotypes, either 50K or higher (some all the way to the HD800K level) on about 3,000 animals,” says Thomas.

“The first phase of this research is genomics. We have also finished an intensive steer project. We fed the steers

with our bulls so that we knew the data collected from our steers would be useful for our genetics program. That project is a big collaboration between the medical school research group in Denver, the veterinary group here at CSU, the CSU Department of Animal Science, and the animal science group at the University of Wyoming,” he says.

“We started PAP-testing steers at a very young age, so we could categorize them as high-PAP or low-PAP, then took them all the way to slaughter. We PAP-tested them multiple times to make sure we had them in the right category, because PAP score can change,” explains Thomas.

When all was said and done, Thomas and his team had three categories of tissues from the steers, including low-PAP healthy animals, high-PAP healthy animals and high-PAP animals that were compromised and unhealthy.

“We are generating a new type of data from these tissues, which we call sequence,” Thomas says. “This is a step beyond what the current beef industry is using in their genomic EPDs. We expect these data to take us to the next step in study and applications of genetics of these traits.”

What we have learned

“As scientists, we find out that the more research we do, the less we know,” Thomas says. “High-altitude disease is something we still have a lot to learn about. PAP is a useful tool, but [it] is not telling us everything we need to know about why some animals tolerate high altitudes and others do not. The DNA information could take us farther.”

Thomas says another important thing coming out of his research is that tolerance to high altitude or animal adaptability is found to be a polygenic trait, not a single gene. A report that came out many years ago said high-altitude disease had some kind of dominant gene action. He says this got

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producers thinking there was some “magical gene” that inferred tolerance to high altitude.

“Our initial DNA research is telling us that this is not true. There are many genes involved,” explains Thomas.

There are 29 autosomal chromosomes and the X and Y, so cattle have 30 chromosomes. Thomas says there are many chromosomal regions involved in inferring tolerance to high altitude.

“It should be noted that many of these chromosomal regions also contain genes involved in inflammation, which could be related to the animal’s susceptibility to BRD,” he says. “What this means to producers is that sometime in the near future they could expect some DNA-testing products to come on the market, but they won’t be single-gene, simple tests. They will be more like the SNP-chip tests that most breed associations are starting to do, either 50K or some other type of high-density genotyping product that can look across all the chromosomes and not just at one specific gene,” he explains.

Thomas says initial analysis of the sequence data would look at what he and his team refer to as “differential expression of genes.” That has progressed to the point that Thomas can do an analysis and look at what all 25,000 genes are doing at any one time.

“This would tell us already that we are looking at more than 1,000 genes in which the level of expression is different between a high-PAP and a low-PAP animal,” he says. “The key word here is polygenic. It’s not just one gene; it’s whole-animal physiology. We are talking about a growing animal, condition of the heart and lungs, etc. There is not one single gene — thank goodness — that regulates all of this.”

Problems at low elevations

Increasing numbers of cattle at low elevations, particularly feedlot animals in the finishing phase, have symptoms or disease conditions similar to high-altitude disease. Thomas says this problem is seen by producers up and down the front range

in Colorado, in areas that aren’t considered high-altitude.

Producers are starting to PAP-test bulls at altitudes less than 6,000 ft. Tim Holt and his veterinary colleagues have found that testing below 6,000 ft. with a low PAP result has proven to not be accurate in predicting future health at high altitudes.

According to Thomas, Joe Neary with Texas Tech University has said that if a producer PAP-tests an animal at less than 6,000 ft. and it has a fairly high PAP, that animal will probably have a high PAP score forever and should not be moved to a higher elevation. If the animal at low altitude has a low PAP, it may or may not have a problem at higher elevation. If you move it to high altitude, he says, you should check it again. If a bull comes from a low elevation, he would need to be tested again at high elevation before you could be sure that he won’t sire calves with this problem.

The problem, now called late-term feedlot death, for lack of a better definition, involves fat cattle that develop pulmonary hypertension and die just before they go to slaughter.

“This is an interesting challenge, and people are wondering if it’s the same condition as brisket disease. We need to do more studies and find out,” says Thomas.

There are several ways to look at this, he says. “A person can hypothesize that it is the same as high-altitude disease and try to

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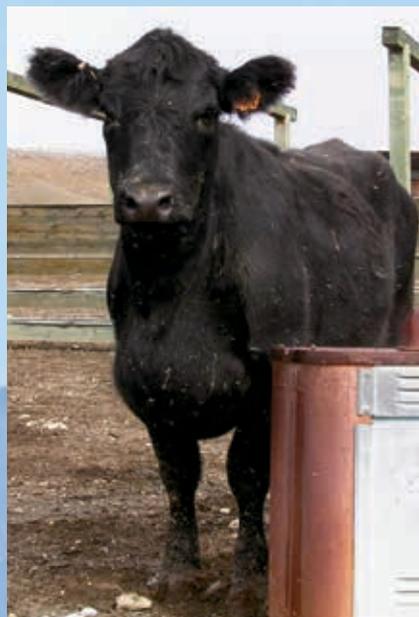


figure out the cause. Did the animal have BRD earlier in life and already has lung damage? Joe Neary made some strong hypotheses in his doctoral dissertation, pointing out that we’ve selected cattle for excessive growth and more muscling, and the heart and lung capacity is not adequate for this kind of animal. We see a similar issue in poultry, called ascites. Is this the same disease? We don’t know.”

Everyone in the mountain states has heard of brisket disease and knows what it is, Thomas says, but late-term feedlot death is something he had never heard of until his arrival at CSU.

“To put it on a timeline, this is a new problem that has arisen in the beef industry, and is something we really need to work on,” he says.

Thomas notes that the research of Joe Neary and Greta Krafusur is important to helping producers and veterinarians understand how much of the condition is due to genetics and/or susceptibility to respiratory disease.

“It will also be interesting to learn how accurately or inaccurately brisket disease is diagnosed or misdiagnosed with other respiratory diseases,” he says. “Researchers at CSU are collaborating with scientists and the USDA facility in Nebraska at the U.S. Meat Animal Research Center (USMARC), studying genetics of feedlot cattle susceptibility to respiratory disease. In these efforts, an interaction among respiratory disease and heart failure is being observed.”

Producers have a lot of time and money invested in cattle by the time they are ready to go to slaughter, and to have them suddenly die at that point is a huge loss.

“Joe Neary’s data from his doctoral studies and the new results from Greta Krafusur’s doctoral research are verifying that as animals get bigger and heavier through the fattening phase, there are some cattle whose PAP scores are increasing — up to risky levels for heart failure,” he says. “This is a very real problem and not something the beef industry can ignore.”



Editor’s Note: Heather Smith Thomas is a cattlegirl and freelance writer from Salmon, Idaho.