Pulmonary Hypertension (PH) in Beef Cattle: Complicated Threat to Health and Productivity in Multiple Beef Industry Segments

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Executive Summary: Three page summary describing challenges of PH and needed research in the beef industry is followed by scientific discussion of 1) cattle health and disease, 2) genetics and genetic evaluation, 3) management recommendations, and 4) needed research.

Pulmonary Hypertension (PH): Pulmonary arteries carry venous blood from the right heart chambers to the lungs so that the blood can be oxygenated. Blood returns through the pulmonary veins to the left chambers of the heart and then pumped to the rest of the body. Pulmonary arterial pressure (PAP) is abnormally high when an animal experiences PH. The right side of the heart responds to the increased work from forcing blood against high PAP. This causes excessive muscle contraction, stretching of muscle fibers, and increased size of the right-side of the heart. When the heart chambers exceed capacity, and its walls thicken, the heart fails and the animal dies. These mortality rates are typically very low even though cattle often experience PH. The consequences of PH on overall health and performance is a growing concern in the beef industry.

Veterinary diagnosis of PH involves inserting a catheter into the pulmonary artery and measuring PAP. Outwardly, the most prominent sign of PH is swelling of the brisket with other signs including lethargy, weakness, decreased appetite, diarrhea, bulging eyes, distention of the jugular veins, swelling of the limbs and under the jaw, and buildup of fluid in the abdomen (ascites). If death occurs, right-sided heart failure is identified during necropsy by enlarged right heart chambers, excessive fluid in body cavities, and liver color (nutmeg) changes associated with the backup of venous blood. Some cattle with high PAP can perform normally, but higher PAP is associated with higher risk of heart failure. Historically, the most common cause of heart failure in cattle was High Mountain Disease (HMD; or High Altitude Disease, or Brisket Disease), caused by low oxygen pressures at altitudes greater than 6,000 ft above sea level. This is most often observed in cow/calf and stocker operations in the mountains. However, a different and more recent problem has been occurring in fattening feeder cattle at moderate altitudes (3,000 to 5,000 ft) and is becoming known as Feedlot Heart Disease (FHD) or Late-Term Death. The signs are similar to HMD because PH helped cause the heart to fail.

High Mountain Disease (HMD) is a condition in cattle raised at high altitudes (> 6,000 ft). The disease has been recognized for over a century in the Western U.S. and research shows a strong relationship between low atmospheric oxygen, development of PH, and right-sided heart failure. The reduced amount of oxygen present in the air at high altitude means less oxygen reaches the

lungs and pulmonary artery, a condition called alveolar hypoxia. This causes the pulmonary artery to constrict (become narrower) and thicken. Arteries in the lungs also thicken. This makes the heart work harder to pump blood and may result in heart failure. Cattle are more prone to developing PH than other species because: 1) the contractive arterial response in cattle is more exaggerated than other species; 2) the design of the bovine lung does not allow free passage of air between intra-lung regions; and 3) cattle have small lung-size to body-weight ratios.

Feedlot Heart Disease (FHD): This condition, which can resemble HMD, has been reported in feedlot cattle since the 1970's. Observation of FHD has been historically very low. At necropsy, right-sided heart failure is clearly a result of PH. This problem has been mysterious because there is knowledge that some affected calves were weaned from ranches of low and moderate elevation and never experienced altitude-associated hypoxia. Some feedlots in the Northern Great Plains at approximately 4,000 ft altitude report up-to 3 percent or higher death losses from heart failure in some groups of cattle. Other anecdotal reports in the Southern Plains suggest that the condition has been seen in feedlots of only 3,000 ft in elevation. We have published data from 15 feedlots at low and moderate altitudes, and the incidence of such losses has doubled over the last decade. Death losses from FHD typically occur late in the feeding period and are therefore very costly.

If PH and heart failure are occurring in steers at moderate altitudes, attributing these cases to high altitude alveolar hypoxia is counterintuitive. What, then explains FHD? Even though it's an extreme example, we know that PH and heart failure occurs in rapidly growing broiler chickens. Research has associated heart failure in poultry with high oxygen demand causing PH as per insufficient heart and lung capacity to grow large breast. In humans, PH is a complex problem with numerous causes, which include metabolic and inflammatory changes that occur with obesity. These predisposing factors in humans and broilers have some of the features of modern, high growth, fattening cattle that in humans would be physiologically categorized as obese by the end of the finishing period. Our studies of growing calves and fed steers support the hypothesis that PH in cattle is caused by more factors than alveolar hypoxia alone. In addition to the effects of altitude on PH, we also see: potential effects from increased animal age and size; features of insufficient heart-lung function; changes in structure of pulmonary veins in addition to pulmonary arteries; abnormal pulmonary venous pressures originating from alterations of the left side of the heart. Our on-going studies are exploring features of FHD that are both different and shared with HMD.

PAP and Genetic Improvement: The trait of PAP is currently measured by veterinarians on ~10,000 cattle per year in the Western U.S. Most of these cattle are replacement bulls and heifers and many are seedstock. Cattle with PAP values $\leq$ 41 mm Hg are considered low risk of developing HMD, whereas cattle with values ranging from 42 to 49 mm Hg are considered moderate and those with values $\geq$ 49 mm Hg are considered high risk. In our research at high altitude, approximately 50% of cattle are in the low risk cattle category, 40% are in the moderate risk category, and 10% are in the high-risk category. It is difficult to measure death loss on most ranches; thus, PAP is used as an indicator of PH and has moderate heritability, similar to weaning weight. Therefore, PAP is an indicator trait for mountainous beef production systems given the economically relevant trait is "survival at elevation". The PAP data are currently being used to calculate an EPD (expected progeny difference) in several breeding programs. Most cattle have an EPD value

ranging from -4 to +4 with some extreme high-risk cattle ranging up to +19 with higher levels being undesirable.
The initial PAP EPD development used data from Colorado State University's John E. Rouse Beef Improvement Center (BIC; elevation ~7,200 feet). Calves were sired by bulls bred and raised in this historic program as well as by prominent Angus-AI sires provided by semen companies (i.e., progeny testing program involving ABS, Select Sires, Genex, etc.). Recent collaborative research with the American Angus Association confirmed that PAP is positively, but weakly, associated with yearling growth traits, suggesting it is possible to identify curve bending bulls that can increase growth rate without increasing PAP. This study also revealed a moderate to strong genetic relationship between PAP collected at altitudes between 4,000 to 6,000 ft and those > 6,000 ft. However, further study is needed to evaluate similar relationships between yearling PAP and PAP measured in fattening feedlot cattle. Furthermore, our initial research using genomic technologies, which is the ability to use information from many genes across the 30 bovine chromosomes, indicate that PAP is a polygenic trait like other performance traits such as weight, backfat thickness, and marbling score. This suggest that PAP is influenced by thousands of genes; therefore, future efforts for genetic improvement will include PAP data as well as thousands of markers on SNP-chips. Like most other traits, these breeding values will be genome-assisted EPD already being published by American Angus Association.

Causes of PH: Cattle have relatively high PAP in comparison to other species and therefore easily develop PH. There is growing evidences that there are multiple causes beyond high altitude hypoxia. Respiratory diseases, which include various forms of pneumonia such as acute interstial pneumonia (AIP), may also be interactive culprits. Also, an animal's overall level of fatness and the interaction of fat with the immune system may be another factor causing PH. Additional research is needed to understand the cause/effect consequences of PH and other diseases such as AIP and bovine respiratory disease (BRD). Also, since PAP is the primary tool to measure PH and cattle innately have relatively high PAP, recent observations of a negative relationship between PAP measured on yearling steers and carcass weight has created concern that there may be subtle, derogatory effects of PH on performance of finishing cattle.

Management and Needed Research: PH and right heart failure in cattle have historically been attributed solely to the effects of high altitude. Therefore, HMD was initially thought as a problem of cattle only in the Rocky Mountain region. While high altitude effects on cattle continue today, we are learning that PH is a much more complex problem than previously recognized. We are now learning that PH is unfortunately important to the entire beef industry because it may be causing reduced performance and losses in late fed cattle through what we term "FHD". Because the long-term effects of PH cause detrimental tissue remodeling in the heart, lungs, and arteries; there are limited options for treatment of these animals. If a calf is suffering at high altitude, taking the calf to lower altitude may provide relief, as do veterinary treatments to reduce swelling, but this may be temporary. The primary way to reduce PH in cattle appears to be through genetic selection using PAP EPD; however, additional research is needed to understand the relationships of measures collected at different locations on the growth curve (weaning vs. yearling vs. finishing) and different levels of gain. This knowledge would improve the usefulness of the EPD. There are no known remedies to deal with the effects of PH in fattening feedlot cattle other than to realize the animal before it enters heart failure. Because there appears to be a vast number of reasons cattle

can develop PH, comprehensive health management prior to, and after, the cattle enter the feedlot is needed to diagnose and manage PH as well as respiratory disease.

Introduction

The U.S. beef industry is comprised of numerous segments including the seedstock, cow/calf, stocker/feedlot, and packer working together to produce beef for the consumer. The initial segments (i.e. seedstock and cow/calf) have thousands of producers across diverse landscapes charged with breeding and producing calves. The industry then becomes more concentrated as cattle move into grain producing regions with cattle feeding operations in the Great Plains contributing approximately 80% of the fattened beef in the US and annually supplying 20% to 25% of the world's beef (Galyean et al., 2011). The US beef industry has been maintaining annual supply by selecting and producing cattle of larger size, while the number of cows in the production cycle(s) recently reached its lowest level since 1952 (~32 million cows; USMEF, 2012). More recently, cow numbers and feedlot placements have increased (http://lmic.info, 2017) due to increases in prices during the period of low cow numbers. Irrespective of the stage of the beef price cycle, profits in beef production systems are often diminished by sickness and death losses and can also be influenced by poor performance. Accumulating evidence suggests that pulmonary hypertension (PH) may contribute to reductions in profit due to increased mortalities. PH is caused by a wide-variety of factors and influences many ages and weight classes of cattle. The likelihood of heart failure increases with severity and rapidity of PH onset. While the apparent incidence of heart failure is very low and poorly recorded in most production systems, the subtle effects of PH on the overall health and performance of beef cattle are concerning and poorly understood.

The goal of this white paper is to provide information to improve understanding of causes and consequences of PH and to clearly delineate the limits of the knowledge related to these health issues in beef cattle. We will also discuss what has been termed, High Mountain Disease (HMD), or brisket disease, typically observed in high altitude cow/calf and (or) stocker systems. The document also compares and contrasts characteristics of altitude-induced PH to heart failure observed in fattening beef cattle in feedlots of low to moderate elevations (i.e., Feedlot Heart Disease, FHD; see photos on the next page). The genetic complexity of PH will also be discussed.

This white paper was composed by a team of scientists with expertise ranging from veterinary medicine to cardiopulmonary pathology and physiology to breeding and genetics of beef cattle. As with other industry professionals, this team struggles with the semantics, and often lack published research, of PH diseases and phenotypes in cattle. We attempt to clarify terminology based on the current status of PH knowledge.

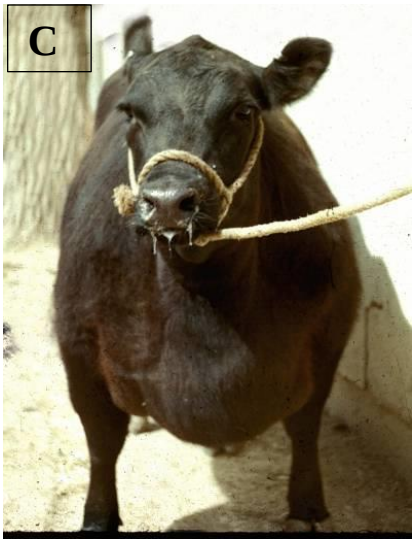

Figure 1. Photos of cattle suffering from pulmonary hypertension (PH). Figure **A** is a steer in a feedlot at 4,100 ft elevation (Feedlot Heart Disease; FHD). Figures **B** and **C** are cattle experiencing PH at elevations above 5,000 ft (i.e., High Mountain Disease; HMD). Note the swelling in the brisket and abdomen.

Consequences of PH and High PAP

Blood pressure is not routinely measured in large animals; however, pulmonary arterial pressure (PAP) is measured in beef cattle and serves as a measure of PH; therefore, PAP is an indicator trait of the tolerance of cattle to high elevation. While many health signs can be suggestive of PH, right heart catheterization to measure PAP is the primary procedure for diagnosing PH in cattle. This trait, PAP, will be discussed later in the section titled: "PH Indicator Trait: PAP." Most mammals have PAP of approximately 20 mm Hg and humans with resting PAP exceeding 25 mm Hg are diagnosed with PH. Cattle, however, are atypical with PAP reported at 34 mm Hg at sea level and over 40 mm Hg at elevations above 5,000 ft (Table 1). The best historic reference describing PAP in cattle is that of Holt and Callan (2007). Note that there is a range of PAP values for the cattle described in Table 1, which provides evidence that there is tremendous variation in the trait; simply meaning that some cattle can accommodate and tolerate a hypoxic environment and some cannot.

The range of PAP measures in cattle is described in Table 1 where grazing crossbred cows sampled at sea-level have PAP values approximately 9 mm Hg higher than healthy humans and other large ruminants adapted to high altitude (i.e., American Bison and Yak). Evidence also suggests that yearling bulls and fattening steers gaining ~3.5 lbs/day have substantially higher PAP values than other types of animals. Cattle have higher PAP than most animals and evidence suggest these values increase when the animals are fed diets for increased rates of gain. The fattening Angus steers in the first row of Table 1 have PAP values within the same range as people suffering from PH (shown in the last row of Table 1). The health consequences and concerns of elevated PAP in fattening steers will be described later in this paper as we discuss "Feedlot Heart Disease". High mountain disease (i.e., brisket disease) has been problematic in the Rocky Mountain region of the U.S. for at least a century (Glover and Newsome, 1915). Figure 2, panel B, illustrates that as a steer ages and moves from a cow/calf operation at high elevation to a feedlot in Eastern Colorado of moderate elevation, PAP values increased (Neary et al., 2015).

Table 1. Review of pulmonary arterial pressure (PAP) measures in cattle and closely related ruminant species and humans.

Animals	Altitude (ft)	PAP (mmHg)	PAP Range (mmHg)	References
Angus fattening steers[1]; n = 50	4,600	54.1 ± 2.7	42-143	Krafsur et al., 2017 Neary et al., 2015
Yearling Angus bulls[1] (gain-test); n = 1,397	7,200	45.8 ± 0.3	29-139	Zeng, 2016 Crawford et al., 2016
Yearling bulls of several *Bos taurus* breeds (gain test); n = 2,426	7,200	45.1 ± 0.8	29-145	Crawford et al., 2017a
Mature Angus cows[1]; n = 44	7,200-9,000	42.8 ± 0.8	31-55	Bailey et al., 2016
Yearling Angus heifers[1] (grazing); n = 3,489	7,200	41.4 ± 0.2	22-135	Zeng, 2016 Crawford et al., 2016
Yearling Angus steers as grazing stockers[1]; n = 773	7,200	41.1 ± 0.2	27-138	Zeng, 2016 Crawford et al., 2016
Angus-crossed cows (*Bos taurus* and *Bos indicus*), n = 49	0 ***sea-level***	34 ± 0.5	28-41	Holt, personal communication
Mature American Bison; n = 6	7,200	29.8 ± 0.8	28-34	Holt, personal communication
Mature Himalayan Yak; n = 6	12,000	20.2 ± 1.4	18-21	Anand et al., 1986
Healthy Human; meta-analysis	≤ 1,200	25	15-35	Bossone et al., 2013
Human hypertension; meta-analysis	≤ 500	>35	15-70	Moraes et al., 2000

[1]Cattle were from Colorado State University Beef Improvement Center (i.e., One Bar Eleven Angus Ranch also known as Rouse Ranch near Encampment Wyoming).

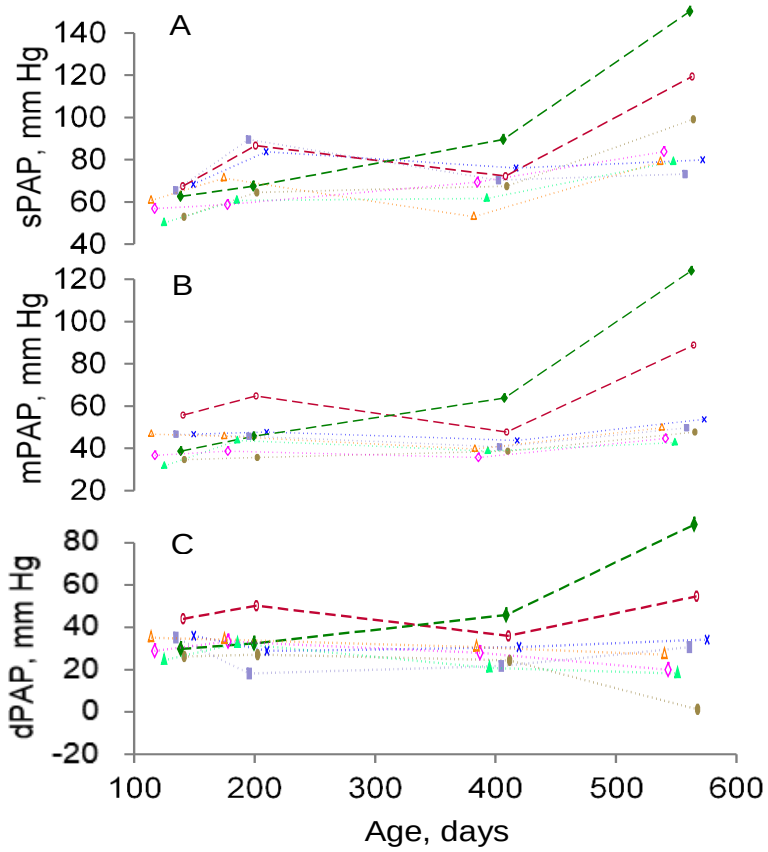

Figure 2. Line graphs showing changes in A) systolic pulmonary arterial pressure (sPAP), B) mean pulmonary arterial pressure (mPAP), and C) diastolic pulmonary arterial pressures (dPAP) for male Angus calves tested at 4, 6, 13 (Group A), and 18 mo of age. Each calf is represented with a different marker and color. Dashed red and green lines represent 2 steers that had noticeably greater mPAP at 18 mo of age than the other 6 steers (n = 8/group). Dotted lines link observations for the remaining 6 calves (Neary et al., 2015).

Terms of PH-Heart Failure

Approximately a century ago, heart failure in high elevation beef cattle came to be known as "Dropsy" because the cattle had accumulation of fluid in the loose tissues under the jaw and brisket in response to hypoxia-induced pulmonary arterial vasoconstriction (Glover and Newsome, 1915). These issues caused the heart to fail and the animal died. The parallel term "Brisket Disease" thus became part of the common language among stockmen in the Western U.S. when swelling of the brisket was observed. The condition has also been coined "High Mountain Disease (HMD)." Signs and symptoms of this disease may include lethargy, weakness, collapse, diarrhea, bulging eyes, jugular distention and pulsation, and most obviously, swelling of the brisket (Holt and Callan, 2007). This condition is precipitated by a drop in oxygen levels in breathable air as altitude increases. Specifically, air at 6,000 ft of elevation has ~80% of the oxygen of sea level and 12,000 ft of elevation has ~63%. Because death rates from PH and heart failure are low, and cattle succumbing are often difficult to locate and diagnose in rugged mountain pastures, PAP is used as an indicator of PH. The use of this trait by the beef industry and its genetic regulation will also be discussed in this white paper.

There are examples of people and animals (i.e., Tibetians, Sherpas, Yaks, etc.) that have adapted to high-altitude hypoxic environments via changes in anatomy, blood hemogram factors, and presence of beneficial alleles in oxygen-responsive genes (Anand et al., 1986; Gilbert-Kawai et al., 2014); however, cattle appear to lack these adaptive mechanisms (Ahola et al., 2006; report of

weak relationship between hematocrit and PAP). Anatomic and physiologic attributes of the bovine lung actually predispose cattle to develop PH and respiratory disease. Cattle are sensitive to environmental hypoxia (i.e., experienced in high altitude) and develop PH indicative of pulmonary artery vasoconstriction. The bovine lung also has substantial amounts of connective tissue covering the surface of the lung and separating adjacent lobules. Thick connective tissue septa can serve to isolate injured and diseased regions in the lung from healthy lobules; however, its presence increases resistance, work of breathing and respiratory rate, increasing exposure of the lower respiratory tract to irritants and pathogens (Tyler et al, 1983). Moreover, compared to other mammals, lungs of cattle have limited alveolar surface area as a proportion of body weight, reduced alveolar macrophages and antimicrobial proteins, predisposing cattle to alveolar hypoxia, PH, and respiratory disease (Veit and Farrell, 1978).

We have preliminary evidence that PH in cattle may predispose feedlot cattle to diseases such as liver abscess, bovine respiratory disease (BRD; although whether BRD contributes to PH, or vice versa has not been determined), and acute interstitial pneumonia (AIP; Gulick et al., 2016). Also, because of the uniqueness of cattle lungs, it should be understood that PH can be initiated for many reasons, which gave us the need to help clarify terms such as High Mountain Disease (brisket disease) versus Feedlot Heart Disease, which is the phrase being introduced in the white-paper. Feedlot pen riders and managers may just use the phrase "Heart Failure" when discussing Feedlot Heart Disease and this condition may not have had anything to do with high altitude. Managing complex diseases are not new challenges to the beef industry. Acidosis and BRD are examples of such diseases. For example, the following review-citations describe at least 5 to 10 causes of acidosis in feedlot cattle ranging from grain processing and sorting, level of feed intake, rumen micro-organisms population, illness, etc.; therefore, acidosis is combatted with comprehensive management, such as proper ration formulation, step-up diets, bunk management, knowledge of the background of the cattle, etc. (Owens et al., 1998; Schwartzkopf-Genswein et al., 2003; Gonzalez et al., 2012; DeVries et al., 2014). Pulmonary hypertension in cattle appears to be caused by a variety of potential contributing factors and interactions amongst those factors and may require approaches that span several segments of the beef industry to minimalize its influences.

PH and Growth Curve

For most of a century, PH was considered a physiological phenomenon solely affecting animals in cow/calf and stocker operations at high elevation (Tucker et al., 1975; Rhodes, 2005). However, we now know that many classes of cattle can experience an increase in PAP attributable to hypoxia-induced pulmonary artery constriction. As presented in Table 1 and Figure 2, PH occurs in cattle and there could be many reasons for hypoxia (altitude, altered aerobic/anaerobic metabolism from fattening, respiratory diseases, etc.). Our recent research has found that PAP measures were greatest in feedlot cattle during the finishing phase at 4,600 ft than in these same suckling calves at an altitude of 7,200 ft (Neary et al., 2015). Therefore, in addition to other factors, location on a growth curve and possibly rate of gain must be considered in interpretation of PAP results.

While hypoxia-induced pulmonary artery constriction reduces oxygenated lung tissue, the phenomenon subsequently causes PH and increases workload on the heart. We now know that the outermost adventitial tissue surround pulmonary arteries and arterioles plays a significant role in

tissue remodeling in the lung and allows infiltration of inflammatory cells and fibrous mediators to stiffen blood vessels in the lung (See Figure 3). In human PH patients, important classes of drugs called vasodilators are typically prescribed to relax stiffened blood vessels. However, these drugs are not approved for use in livestock; thus, calves suffering from hypoxia are relocated to lower elevations as a remedy. While many calves recover, some calves have extreme/out-of-proportion PH that cannot be explained by altitude-hypoxia alone. Therefore, it was not surprising that Neary and colleagues (2013) reported that heart failure deaths in preweaned beef calves at several high elevation ranches was higher than the national average. Many of the calves in this study also suffered from other illnesses such as respiratory diseases. Therefore; future research needs to investigate the potential interactive relationships between altitude-induced hypoxia and respiratory illness. Spirometry measures (i.e., lung function measured by flow and volume of air) commonly measured in studies of altitude-induced hypoxia are also measured in studies of cattle suffering from BRD (Bureau et al., 2001ab); therefore, revealing a great challenge to differentiate between the two health issues.

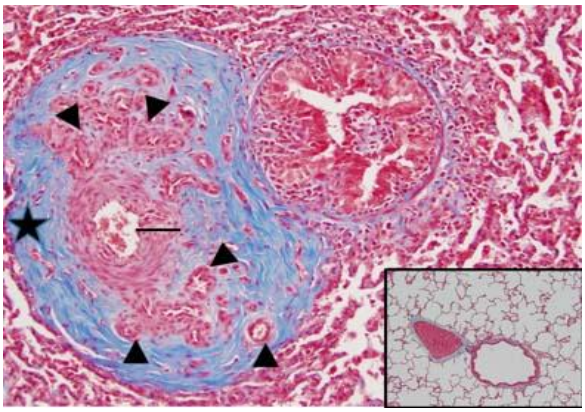

Figure 3. Lung tissue from a calf with altitude-induced PH. Hypoxia-induced smooth muscle hypertrophy, intense adventitial fibrosis, and massive vessel in-growth (vasa vasorum hyperplasia) are common in these calves. The newly formed vessels allow inflammatory cells and mediators to cause blood vessel remodeling. The photo inset at the bottom right is from a normal/healthy steer living at high elevation.

Shirley and co-workers (2008) studied genetic relationships between PAP measured at weaning and measures of growth in an Angus breeding operation in Colorado (i.e., Ty-Bar, Carbondale, CO, 6,500 ft elevation). Some positive relationships were observed between PAP and growth traits in these 6 month-old calves; however, other data from calves sampled at weaning is limited. Most cattle that receive a PAP measure are close to a year of age or older and are typically the potential replacement bulls and heifers for high altitude ranches. In the Western U.S., the veterinary community PAP tests approximately 10,000 herd replacements per year as PAP is known as an economically relevant indicator trait for PH (Kessler et al., 2017). The indicator trait of PAP collected from yearling cattle will be discussed in-depth later in this white paper.

Neary and co-workers (2015) conducted research evaluating PAP in fattening Angus steers that were 18 months of age (i.e., fattened steers at the flattened-top of the growth curve; Figure 2). Very interestingly, and as stated previously, we found that PAP measures were greatest in feedlot cattle during the finishing phase at 4,600 ft than in these same suckling calves that were first measured at an altitude of 7,200 ft at 4 months of age. These calves were born and weaned at Colorado State University's Beef Improvement Center (i.e., Rouse Angus Ranch) at an altitude of 7,200 ft (i.e., east of Encampment, WY). The cattle finished at the Eastern Colorado Research Center (ECRC), in Akron, CO (~4,600 ft elevation). Moderate to strong correlations were observed in PAP levels in Angus calves measured at 6, 13, and 18 months of age; therefore, if a calf had a

high PAP measure at weaning (6 months) or yearling age (12 to 13 months) at a mountainous cow/calf operation, they were likely to have a high PAP level at 18 months of age when they were fattening in the feedlot at moderate elevation. However, none of these 18-month-old fattened steers exhibited symptoms of PH, although the average PAP for these steers was > 50 mm Hg and considered high-risk for heart failure. Quality grade for these 119 Angus steers were within the norm of the industry (i.e., 10% prime, 83% choice, and 7% select). Findings from this study raised questions regarding health, performance and carcass characteristics in cattle with PH, as the cattle had no observable signs of progression towards heart failure. These results stimulated the basis for future studies in fattening feedlot cattle.

For greater than 100 years, High Mountain Disease was described as stiffening of the pulmonary artery that led to remodeling and failure of the right ventricle of the heart. While these observations still hold true for cattle experiencing PH as a response to altitude or, alveolar hypoxia arising from chronic respiratory disease, Feedlot Heart Disease is observed in fattened cattle at modest elevations (< 5,280 ft; cattle at the top-flattened portion of the growth curve). This observation potentially defies industry and scientific assumptions that low altitude populations of cattle are highly unlikely to suffer heart failure. A 1974 survey of 4 Colorado feed yards (elevation ~5,200 ft) identified cattle with symptoms and postmortem lesions compatible with PH progressing to right-sided heart failure in 116 out of 1,988 yearling cattle (5.8%) with disease more commonly occurring during the latter half of the feeding and fattening period. Acute pneumonia was a common complication or co-illness in these cattle. The risk of right-sided heart failure was 2.85 cases for every 10,000 head of cattle placed in these feed yards (Jensen et al. 1976).

While heart failure in feedlot cattle appears to be associated with remodeling in the pulmonary arterial circulation and right heart ventricle, these cattle also have evidences of alterations in the left heart ventricle and pulmonary venous circulation. Our first discussion of this potential phenomenon was alluded to in Neary et al. (2015) and has become the focus of the PhD Dissertation research of Dr. G. M. Krafsur (see most recent abstract; Krafsur et al., 2017). It's possible that these cattle are likely experiencing PH secondary to left-sided heart disease, similar to obese humans with mitral valve disease or left ventricle dysfunction (Robbins et al., 2009; Barnett and Selby, 2015). Strong similarities have been noted between body mass morphometrics (height and weight) of obese humans and fattened cattle. Specifically, percent body fat levels of low to medium choice beef carcass quality grades are similar to overweight individuals (body mass index = 25 to 29.9) and a high choice or prime grade beef is similar to an obese individual (body mass index > 30; Hallford et al., 1976; Wagner et al., 1988; Yelich et al., 1995; Erselcan et al., 2000; Ogier et al., 2002).

It has been speculated that cardiopulmonary disease associated with growth enhancement in beef cattle may parallel observations in fast-growing broiler chickens raised at low altitude. Structural and functional alterations in the left ventricle of the heart of fast growing broilers are involved in development of ascites (also known as Sudden Death Syndrome or Flip Over Disease), which precedes PH and right ventricle failure (Olkowski et al, 2001, 2005). The syndrome observed in poultry that have excessive large breast may be much more extreme than that observed in beef cattle. There are limited studies of the ratio of heart size in beef cattle relative to their overall body or carcass weight in recent literature. In historic studies, results suggested that as cattle get larger, so do all categories of muscle, which includes the heart (Holliday et al., 1967; Berg and Butterfield,

1976). Concomitantly, this is not true for the size of the bovine lung relative its overall body size. Specifically, Gallivan et al., (1989ab and 1991) described limitation of the pulmonary system of the cow relative to other animals such as the horse. Specifically, a fast growing beef calf at reset has twice the oxygen consumption of a horse and yet possess less than 30% of the horse's lung volume. Because the heart and lung interact through integrative physiological mechanisms, additional studies involving growing and fattening cattle are needed to understand the relationships between growth, fatness, and PH in cattle as to develop comprehensive breeding and management strategies for healthfulness as the calf grows from the cow/calf and stocker segments to the finishing phase.

Incidence of Disease

In a study of 10 Canadian feedlots, the incidence of death due to right-sided heart failure doubled between the years of 2000 and 2012 (Neary et al., 2016). Eleven cattle died of heart failure and 45 cattle died of digestive disorders for every 10,000 cattle entering the feedlot. Given that cattle were four times more likely to die of a digestive disorder than heart failure, on first impression it appeared that heart failure was a relatively insignificant problem. The death losses in these feedlots were less than in the report of Jensen et al. (1976), which involved cattle in Colorado feedlots. These feedlots described by Neary et al., (2016), however, were located at elevations < 4,300 ft (1,300 m; Figure 4), which is not a high-altitude environment. Therefore, creating concern for the influence of moderate altitude on the health of fattening and finishing cattle.

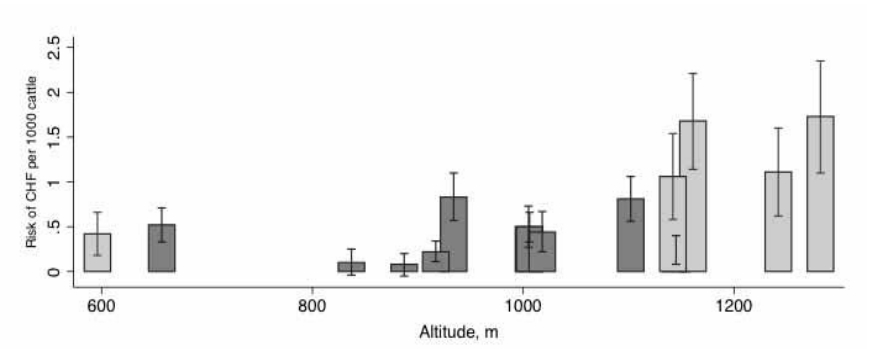

Figure 4. Risk of congestive right heart failure (CHF) per 1,000 cattle entering US (pale) and Canadian (dark) feedlots according to altitude (Neary et al., 2016).

Death from altitude-induced PH in cow/calf and summer stocker operations has been documented for approximately a century (Glover and Newsome, 1915). Holt and Callan (2007) reviewed the incidence of these types of death and suggested that calf losses of 3 to 5% could be expected in high elevation production systems of native cattle. Will and Alexander (1970) reported a slightly lower incidence of 0.5 to 2% of cattle native to elevation of ≥ 7,000 ft or higher, but the incidence rate could increase to 10 to 40% for cattle transported from low to high elevations. Salman et al. (1991) reported similar incidences. Death loss observations in the Angus cattle at Colorado State University Beef Improvement Center are much less than these reports (Crawford et al., 2016). This could partly be due to genetic improvement for PAP; however, AI sires are used in this herd that have not been selected for low PAP; therefore, the low incidence rate could also be due to the diligence of identifying cattle with high PAP and culling them. In this production system and once high PAP yearlings are culled from the herd, the number of cattle observed with symptoms of PH is negligible.

Additional Diseases caused by PH and Possibly Reduced Feedlot Performance

Perhaps, the greatest impacts of PH on beef production are the unrecognized detrimental results of this phenomenon on health and productivity. First, consider the effects of right ventricular enlargement and dysfunction that occur secondary to PH on other organs. A physiological consequence of PH is an increase in preload or venous congestion. The Starling law of the heart states that an increase in preload, or myocardial stretch, is necessary to maintain stroke volume, and therefore cardiac output, in response to an increase in afterload. In other words, PH leads to venous congestion. Right ventricular dilation occurs secondary to an increased preload. Because the heart is surrounded by a poorly distensible pericardial sac, the result is left ventricular compression and impaired function. This leads to systemic hypotension, or low blood pressure (Hecht et al., 1962). An increase in venous pressure and a reduction in systemic arterial pressure means that there is now a reduced driving pressure for blood flow to peripheral tissues. Organs with higher basal metabolic oxygen requirements, particularly the kidney, liver and the gastrointestinal tract, that are relatively hypoxic under normal physiological conditions are especially predisposed to injury as a result of hypotension. In a recent study, central venous pressures, a measure of venous congestion, were found to be positively associated with the risk of liver injury in feedlot steers (Gulick et al., 2016). These findings suggest that liver abscesses may be attributable to a "two-hit" mechanism: rumen acidosis and gastrointestinal hypoxia.

A second, and perhaps even more significant, consequence to PH (or cause) is BRD and AIP, which is an acute respiratory distress syndrome (ARDS) of unknown cause. By definition, swelling due to left ventricular failure or fluid overload cannot be the primary cause of respiratory failure for a diagnosis of AIP (ARDS, 2012). Distinguishing between left-sided heart failure and ARDS, is not straight forward (Gehlbach and Geppart, 2004), particularly because high pulmonary arterial wedge pressures often co-exist in cases of ARDS (Ferguson et al., 2002). Pulmonary arterial wedge pressure is a measure of left atrial pressure and indicative of pulmonary edema (i.e., buildup of fluid in the lungs); therefore, wedge pressure is indicative of an increase in response to pulmonary venous hypertension, left ventricular dysfunction, or both. The potential contribution of pulmonary venous hypertension to PAP was first reported in the 1960's (Kuida et al., 1963). Further investigation of these types of pressures (i.e., wedge pressures) are needed to better understand PH and the bovine lung as it may not be coincidental that AIP (Lonergan et al., 2001) and heart failure (Neary et al., 2016) both occur during the feedlot finishing phase. Also, additional research is needed to understand the whether BRD contributes to PH, or vice versa.

Productivity losses, independent of mortalities, due to PH are only now becoming known. A study of a decade of Angus steer data from the CSU-BIC revealed a derogative relationship from PH, as indicated by PAP and carcass weight (Figure 5). Specifically, regression analysis of hot carcass weight (HCW) and PAP, was a negative relationship. A negative correlation was also observed ($r = -0.33$; $P < 0.05$) in the 10.7% of the steers categorized in the high PAP group. Note the differentially skewed distributions of the two traits (Figure 5). In brief, we found a large group of steers in the PAP designated low and moderate risk categories for heart failure near the mean and then a tail of high risk animals (i.e., steers with PAP > 49 mm Hg). This high-risk group had approximately 33 lb reduction in carcass weight relative steers in the low and moderate health risk categories based on PAP score. This ~33 lb reduction in carcass weight could equate to a loss of

~$66/steer (based on choice, yield grade 3 average carcass value in spring 2017). This is a conservative estimate and one of many feedlot performance traits that could be added to losses accrued from FHD. These results support the report of Kessler et al. (2017) that described the dollar value of PAP in yearling bull purchases. Further study of the economic relevance of PH across the segments of the beef industry is needed to understand the impact of PH on performance of cattle.

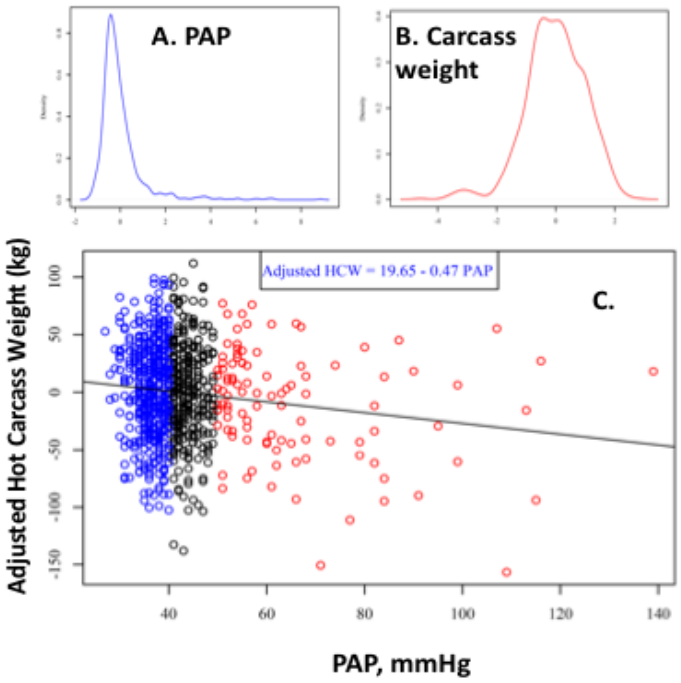

Figure 5. Panels **A** and **B** are distribution of PAP (mm Hg) and hot carcass weight (HCW; kg; n = 903). PAP measure is the yearling phenotype collected at CSU-BIC (7,200 ft) with carcass weight collected post-fattening at Eastern Colorado Research Center (4,600 ft). Panel **C** is the regression of HCW on PAP adjusted for age, contemporary group, and slaughter date. PAP values are stratified as low, (blue), moderate (black), and high, (red symbols) (> 49 mm Hg). All terms in this model were significant ($P < 0.05$). In these steers, PAP averaged 42.1 ± 0.4 mm Hg and carcass weight averaged 856.6 ± 3.4 lbs.

PH Indicator Trait: PAP

To our knowledge, there are no data collection systems for mortalities resulting from PH in cattle. This is due to limited access to cattle in large and rugged pastures in mountainous beef production systems and more recently with increased incidence in the feedlot sector, due to the need to improve diagnosis in fattening-feeder cattle. Because of this challenge, PAP is used as an indicator trait to determine if cattle are tolerant of the hypoxic conditions that can result in PH. Mean PAP is estimated from the collection of systolic and diastolic PAP measured within the pulmonary artery. These measures are collected from cattle in a squeeze-chute by a veterinarian that developed specific skills. To effectively measure this phenotype in cattle at high altitude, recommendations are that the cattle reside at an elevation greater than 5,000 ft for at least 3 weeks. Relevant to measurement of PAP, this phenotype is also influenced by sources of variation such as breed, gender, pregnancy, age and weight, elevation, concurrent and (or) previous illness, environmental conditions (e.g. temperature), etc. (Holt and Callan 2007). These sources of variation will be discussed later, with implications as to appropriate use of data for genetic evaluation.

In the Rocky Mountain region of the United States, PAP is annually measured on > 10,000 potential replacement bulls and heifers. Many beef producers use the raw phenotype to cull high

risk cattle. Current recommendations are that cattle with PAP values ≤ 41 mm Hg be considered low risk for development of HMD (heart failure), whereas cattle with values ranging from 41 to 49 mm Hg are considered moderate risk. Cattle with values ≥ 49 mm Hg are considered high risk of developing HMD (Holt and Callan, 2007) and should likely be culled from the breeding program if not completely removed from high elevation environments. PAP is not currently used in the feedlot segment to predict risk of PH other than in preliminary research associated with this issue. Colorado State University manages a research facility to study performance and adaptability of Angus cattle in high elevation beef production systems. This research facility is known as the Colorado State University John E. Rouse Beef Improvement Center (i.e., Rouse Angus Ranch, Encampment, Wyoming). This facility is a seedstock and cow/calf operation that raises its own replacement females, has grazing lands that range from 7,200 to 9,000 ft in elevation, holds an annual commercial bull sale, and supports 420 mother cows and associated animals (e.g., bulls, replacement heifers, stocker-steers, etc.). This organization uses estrous synchronization and artificial insemination (AI) technologies to coordinate a progeny testing program involving the companies of Genex, American Breeder Services, and Select Sires. Each of these companies recommend bulls for potential evaluation of tolerance to high altitude. Limitations to sires tested are primarily due to numbers of available cows and appropriate genetic levels of performance in economically relevant production traits (e.g. calving ease, milk, etc.). In the past 15 years, > 300 registered American Angus Association AI sires have been mated in this program. There are several groups of Angus cattle from the Rouse Angus breeding program described in Table 1. The distribution of the PAP data from this herd appears to have an out of proportion right tail of elevated pressures (Figure 6), which is similar to the steer data on harvest animals from this herd in Figure 5. Therefore, approximately 50.8% of the cattle would be categorized as low risk, 38.1% as moderate risk, and 11.1% as high risk for developing PH and subsequent heart failure.

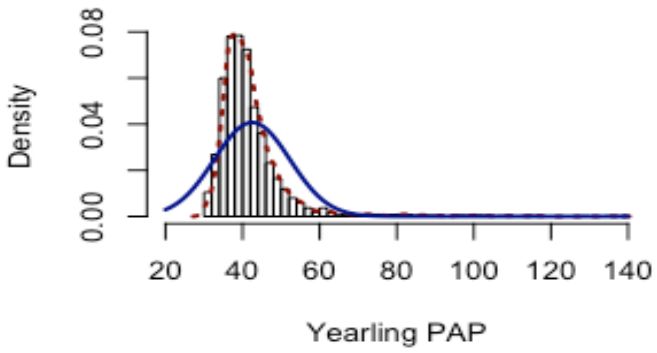

Figure 6. Histogram of PAP (mm Hg, x-axis) in yearling Angus bulls, heifers, and steers (n = 5,659) studied at the Colorado Beef Improvement Center (i.e., Rouse Angus Ranch; elevation 7,200 ft; Zeng, 2016). The y-axis is the percentage (density) of the number of animals at each level of the PAP phenotype (i.e., x axis). Red dots (•) denote density cuve of the data, whereas the blue line simulates normal distribution; therefore, the slight non-normal distribution is observable vs the histogram of each each category (Zeng, 2016).

Genetics and Genetic Evaluation of PAP

Pulmonary arterial pressure was reported to be a trait of moderate ($h^2 = 0.34$) to high ($h^2 = 0.46$) heritability using data from a registered Angus herd in Carbondale Colorado (elevation 6,500 ft; Enns et al. 1992; Shirley et al. 2008). Using data from the Rouse Angus herd (CSU-BIC), which are purebred, unregistered Angus cattle, a moderate ($h^2 = 0.26$) heritability was estimated (Crawford et al. 2016) with a genetic correlation of 0.67 observed between yearling (365 days of age) and weaning (205 days of age) PAP in the Dissertation of Zeng (2016). This result suggests that the genes that influence PAP at weaning have a relatively strong relationship and influence on PAP at a year of age in high elevation production systems. However, the data needed for statistically-sound estimation of relationships between weaning or yearling PAP and similar measures in finishing beef cattle is currently lacking.

Slight to moderate, and positive genetic correlations (≤ 0.22) were observed between growth traits and yearling PAP in the studies of Crawford et al. (2016) and Zeng (2016) using data from Angus cattle from the CSU-Beef Improvement Center; however, stronger relationships (≤ 0.50) were reported by Shirley et al. (2008) using data from the Ty-Bar Angus herd. Pauling (2017) expanded studies of heritability and genetic correlations in Angus cattle with resources from the American Angus Association, Dr. Tim Holt (DVM), and the CSU-Beef Improvement Center as shown in Table 2. The positive, yet weak, genetic correlations among PAP measures and growth traits parallel the findings described by Crawford et al. (2016) and Zeng (2016). In the study by Pauling (2017), however, maternal genetic effects on birth weight were highly correlated to PAP (0.56) but a sound biological relationship for this estimate is yet to be determined. That estimate may be an artifact of the pedigree structure associated with the data used in the study. As such, that relationship should be confirmed via analyses with data from additional populations. These results suggest that breeders should use caution when aggressively selecting for growth traits; however, with these weak, genetic correlations, it should be relatively easy to identify curve-bending bulls (i.e., bulls with ample values for growth that do not have excessively high PAP values).

Table 2. Descriptive statistics of mean pulmonary arterial pressure (PAP) observations by source of Angus cattle (Pauling, 2017).

Source	n	Minimum	Mean	Maximum	SD
AAA [1]	4,511	30	43	180	10.72
CSU-BIC [2]	5,344	22	42	139	9.79
TH [3]	4,810	31	44	164	11.94
Combined	14,665	22	43	180	10.83

[1] American Angus Association
[2] Colorado State University Beef Improvement Center
[3] Dr. Tim Holt, DVM

Interestingly, when the PAP data were divided into the grouping of high (> 5300 ft) or moderate (3,300 to 5,300 ft) altitude, h^2 estimates of the two groups were 0.34 and 0.29, respectively. The genetic correlation was strong between the two measures ($r_g = 0.83$); however, it must be noted that these cattle were primarily tested on ranches along the Front Range of the Rocky Mountains and in Eastern Colorado with altitude ranging approximately from 4,000 to 9,500 ft. Data on the extreme ranges of sea level to 14,000 ft were not available. Recent subsequent analysis of these

data using newly developed statistical techniques indicate that the genetic relationships amongst PAP at various elevations range from 0 to near 1 with heritability estimates ranging from 0.28 to 0.49 at the various elevations (Speidel, 2018, pers. comm.). Encouragingly, evidence of genetic variation suggests use of PAP measures at moderate elevations, although the genetic correlations suggest that some elevations provide more valuable information than others; therefore, we expect that the PAP EPD being developed by the American Angus Association to be a multi-trait genetic evaluation. The moderate PAP measures will contribute information to the primary trait, which is PAP collected at high elevations (i.e., > 5,300 ft).

Table 3 presents the results of a 5-trait model estimating genetic parameters for PAP and carcass traits from the data described in Table 2. Interestingly, a weak and positive (unfavorable) relationship was observed between PAP and ribeye area. These results and the relationships presented in Figure 5, suggest a need for further research addressing the relationships of PH and performance in finishing cattle as the data tabled below and used to determine relationships were collected from yearling seedstock cattle.

Table 3. Heritabilities (diagonal; SE) and genetic correlations (above diagonal; SE) from the 5-trait model for mean pulmonary arterial pressure, back fat, ribeye area, intramuscular fat, and rump fat from American Angus Association data (Pauling, 2017). Note these data were from measures of yearling registered cattle.

Trait [1]	PAP	BF	REA	IMF	RUMP
PAP	0.21 (0.04)	-0.03 (0.12)	0.24 (0.12)	-0.04 (0.10)	0.10 (0.11)
BF		0.43 (0.05)	0.12 (0.10)	0.08 (0.10)	0.70 (0.05)
REA			0.30 (0.04)	-0.31 (0.10)	-0.08 (0.10)
IMF				0.35 (0.04)	0.12 (0.09)
RUMP					0.47 (0.05)

[1] PAP = mean pulmonary arterial pressure; BF = ultrasound back fat; REA = ultrasound ribeye area; IMF = ultrasound intramuscular fat; RUMP = ultrasound rump fat.

Colorado State University's Center for Genetic Evaluation of Livestock (CSU-CGEL) has calculated expected progeny difference (EPD) for PAP for several cattle breeding programs in the western states. For the two Angus breeding programs described in the previous paragraphs, genetic trend showed slight improvements in PAP. This was most likely a result of the unique numeric distribution of PAP where pressures have limited lower physiological threshold (Figures 5 and 6), the continuous introduction of new sires through the progeny test program (a considerable influence in the CSU-BIC as most females are inseminated to sires from low elevation), and (or) a selection program that typically only culls medium and high-risk animals. In general, 90% of the animals will have an EPD ranging from -4 to +4, with the remaining 10% increasing up to +19 mm Hg (note: high PAP EPD are not desirable).

The underlying physiology of this trait and its interaction with altitude suggest that there is likely a limit to genetic reduction of PAP as measured; therefore, Zeng (2016) conducted research evaluating genetic correlations among PAP and growth traits, heritability, and EPD using the categorical veterinary-derived risk descriptions of PAP (i.e., low, moderate, and high). The overall results of this effort were very similar to those obtained using the raw phenotypes. Categorical EPD are often difficult to interpret; therefore, the decision was made to continue to calculate the

EPD using the raw data with mm Hg as the unit of the PAP EPD because breeders and bull buyers in this region of the world are very familiar with the phenotype of PAP. The next step in evolution of this EPD is to combine these data with genomic information (i.e., genome-enhanced EPD) an effort currently underway using CSU-BIC data and genotypes.

PAP is Polygenic

Pulmonary arterial pressure data is currently being used for EPD calculations of traits indicative of tolerance to high altitude in cattle. There are no data collection systems for incidence of high altitude disease as collection of "death" data is difficult on ranches where predators and topography may mean deaths are never observed or observed long after death occurred. To date, 3,000 cattle from the Rouse Angus herd have been high density genotyped (i.e., 50,000 single nucleotide polymorphism (SNP) or greater). Genome-wide association studies (GWAS) have been performed to identify quantitative trait loci (QTL; i.e., places on chromosomes harboring important genes and markers for PAP). Figure 7 presents association results of PAP phenotype and genotypes in weanling Angus steers (i.e., 6 months of age; Neary, 2014) where each chromosome is represented by a different color and dots representing a SNP rising from the x-axis. The further the dot from baseline, the greater the effect on PAP with dots above the line significantly influencing PAP. In this case, the plot looks like the skyline of Manhattan, NY and indicates there are many locations across the 30 chromosomes that are associated with PAP. The conclusion is that the trait is very polygenic (i.e., PAP is regulated by many genes).

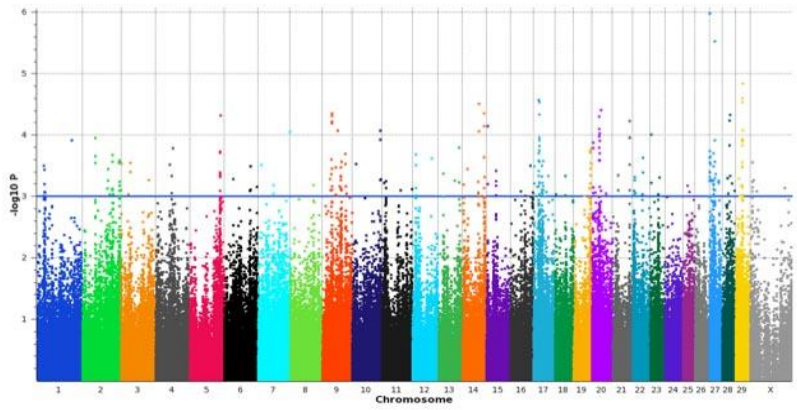

Figure 7. Manhattan plot of mean pulmonary arterial pressure (mPAP; y-axis) in weanling Angus calves (n = 66) at 7,200 ft. Genotypes were from BovineSNPHD (770,000 SNP) and were used in a single SNP analysis (Neary, 2014).

Since current PAP EPD calculations primarily use data collected from yearling cattle, a study was conducted to obtain gene expression data from yearling steers being grown as contemporaries to the gain-test bulls at the Rouse Angus ranch. This study involved identifying high- and low-PAP steers so as to obtain RNA from muscle (i.e., right and left heart ventricle and longissimus dorsi) and the pulmonary tissues (pulmonary artery, aorta, and lung). This approach allowed study of genes and their expression level when the cattle were consuming a bull test ration. The gene expression technology involved RNA sequence so it can also be used for within gene marker discovery. The initial results of this effort suggested that more than 1,000 genes were differentially expressed between high and low PAP steers in the right ventricle of the heart (Canovas et al. 2016). Again, this is evidence that the indicator trait of PAP is polygenic and will require genome-enhanced (i.e., thousands of markers) EPD procedures for genetic improvement rather than selection for a single gene.

These 1,000 genes were involved in gene-pathways associated with immunity, tissue remodeling, and metabolism. There were some responses between the high and low groups that differed in the hypoxia inducible factors (HIF), a large and complex family of 6 genes. A few research groups have studied one gene of this family known as $HIF_2\alpha$ (i.e., also known as EPAS1; Newman et al., 2015; Heaton et al., 2016) suggesting it may be the primary influence on PAP; however, our initial research with a marker described in this publication had no relationship with PAP measures from Angus cattle of several high elevation ranches (Crawford et al., 2017b). At the present, we do not have data from feedlot cattle to test the association of markers within this gene and PAP phenotypes. Nonetheless, the overall results of this study suggest that PAP, as an indicator trait of PH in cattle, is very polygenic and will require SNP-chip based genomic predictions currently used by the American Angus Association's, Angus Genetic, Inc. for other EPD efforts.

Management to avoid or alleviate PH

In beef production systems at high altitude, genetic selection for low PAP EPD is an effective procedure to reduce the negative influences of PH, especially given the moderate heritability of the trait. There are >10,000 cattle tested annually in the western U.S. for PAP. To stay current, veterinarians participate in a continuing education and certification program held at Colorado State University every two years. In addition to measurement of PAP, veterinarians attend educational programs to enhance understanding of all aspects of PH including; history of the disease, pathophysiology, diagnosis, disease management and genetic improvement through PAP testing and use of PAP data and EPD.

A number of other factors may increase PH at high elevation. Studies clearly indicate differences amongst breeds, and like most breed-level studies, there is great variation within breed for tolerance to high-altitude environments based on PAP (Crawford et al., 2017a; Culbertson, et al., 2017). Extreme cold also appears to increase PAP; thus, is a concern to veterinarians conducting PAP tests on yearling bulls during the colder months when breeders are preparing for spring bull sales in the Rocky Mountain states. Also, and as we have recently learned from PAP testing in steers in feedlots, rate of gain may also influence PAP; however, this subject needs additional investigation.

Regarding development and publication of a PAP EPD, there are many important considerations. First, our multi-omics analyses indicate that PAP is a polygenic trait, which requires SNP-chip genotyping for estimation of a genome-enhanced EPD. Also, the PAP phenotype is typically only measured on yearling cattle; therefore, we are challenged to know how these data relate to PAP in baby calves or fattened long-yearling steers. Nonetheless, CSU and American Angus Association are accumulating genomic data, which could be used to assist breeding value estimation in young cattle by collecting DNA samples shortly after birth. Lastly, we know that there are breed influences on PAP (Crawford et al., 2017a; Culbertson et al., 2017); thus, like all EPD efforts, understanding these effects as well as the best way to account for heterosis is needed to help improve healthfulness in commercial cattle.

Unfortunately, once cattle develop symptoms of heart failure (swelling of the brisket, distension and pulsation of the jugular vein, etc.) there are few options. The best possible strategy for

mountainous ranches is to take the affected animal to lower elevation. Success is often indeterminate as the animal may (or) may-not recover and often the stress associated with transport may further compromise the animal. Other possible treatments include the administration of a diuretic (to reduce swelling/fluid accumulation) and broad-spectrum antibiotics. The success of this approach has not been validated and unfortunately follows other options with typically low success rates.

A feedlot animal suffering from heart failure may be condemned at slaughter. Therefore, it best to realize the animal before it reaches a compromised state. An alternative is to euthanize the animal and gain valuable information to guide future management decisions through a postmortem examination determining the cause of death. Heart failure secondary to PH must be differentiated from other causes of heart failure. This information can be used to determine whether heart failure cases clustered in animals that were purchased from a particular source and (or) if the disease was associated with other illnesses. Epidemiological findings indicate that feedlot cattle treated for pneumonia are 3 times more likely to develop heart failure than untreated cattle (Neary et al., 2016). This suggests that comprehensive health management programs will contribute to lowering the incidence of heart failure secondary to PH. Therefore, sourcing pre-conditioned cattle for feedlot placement is logical; however, this may not alleviate PH. This discrepancy is strong justification for additional research to understand the effects of PH on cattle health and interactions with other diseases such as BRD, AIP, etc.

Needed Research

Based on the information summarized in this white paper, it is apparent that PH is a complicated disease in cattle caused by many factors. The incidence of death from PH is low; however, there is great concern that the incidence is increasing and that PH causes, or interacts with, other diseases that negatively influence overall health and performance. There are obvious gaps-in-knowledge, especially as we consider that there is considerable research and production data from yearling Angus cattle, but limited studies on fattening cattle. Therefore, we propose the following research areas be pursued:

1. Determine age-dependent genetic relationships of PAP and PH as an Angus animal ages from a weanling to a yearling in a cow/calf operation and subsequently on to a finished steer in a feedlot. More knowledge about relationships of heart, lung, and body size and carcass traits are also needed.
2. Improve knowledge of both High Mountain Disease (HMD) and Feedlot Heart Disease (FHD). Specifically, we need further knowledge of the unique versus similarities of the diseases and the tools needed for diagnosis and treatment. We also need to know if BRD is a cause, or a consequence of these diseases.
3. Determine breed and subspecies (taurine vs indicine) differences in PH in cattle as they are managed through various production systems.

The first point is crucial, as to gain the knowledge needed for development of EPDs, which need to be expressed at specific age-points on the growth curve, or at a minimum, reveal genetic relationships of various ages. The latter was observed between weaning weight (6 months) and yearling weight and resulted in PAP at various ages merged into a single EPD (Zeng, 2016). The

second item would require, in our opinion, collection of feedlot PAP data on animals genetically related to animals with high elevation PAP observations. This would be an important start to determining these relationships. These types of analyses typically require 1,000 PAP observations on feedlot animals to estimate the genetic relationships amongst PAP (indicator of PH) observations in cattle in the cow/calf and stocker segments at high altitude and feedlot segment at moderate altitude. Determining this relationship in feeder calves weaned from low to moderate elevation production systems and the feedlot is also needed.

Acknowledgements

The writing and data summary within this report supported by Certified Angus Beef, LLC.

Research in this report supported with funds from NIH-5-PO1 HL014985-40A1 (Stenmark) and the John E. Rouse Endowments of Colorado State University (Thomas, Enns, and Speidel). Dr. G. M. Krafsur was also supported by the W. D. Farr scholarship program of the National Cattlemen's Foundation as well as the NIH Training Program (T32 HL007171). Dr. A. Canovas was initially supported by the Fulbright Scholars Program.

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