THESIS

PULMONARY ARTERIAL PRESSURE: REPEATED MEASURES AND DYNAMICS DUE TO CHANGES IN ALTITUDE AND AGE

Submitted by

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ABSTRACT

PULMONARY ARTERIAL PRESSURE: REPEATED MEASURES AND DYNAMICS DUE TO CHANGES IN ALTITUDE AND AGE

High Altitude Disease (HAD) in cattle is a consequence of pulmonary hypertension (PH) induced by hypoxia at elevations > 1,500 m. Pulmonary arterial pressure (PAP) is a phenotypic indicator of animal susceptibility to PH and HAD and is moderately heritable (h^2 = 0.26 to 0.34). The goal of this thesis was to evaluate repeated measures of PAP and dynamics. This goal was achieved with two studies and three objectives: 1) to explore and estimate correlations between different ages and elevations, 2) to determine usefulness of yearling moderate altitude PAP in beef bulls that are transported to high elevation for short- and longer-term management, and 3) to determine usefulness of feedlot entry PAP to additional PAP measures as the cattle approach finishing and harvest. The objective of Study I (Chapter 3) was to determine significant variables and estimate correlation between PAP measurements at moderate altitude and high altitude at differing ages. This scenario often occurs in the Western U.S. beef industry. Data consisted of breed, sire, mean PAP (mPAP) measures at each collection date, elevation, and bull age, from 2017-2019 (n = 89) spring-born bulls at the Colorado State University (CSU) Agriculture Research, Development, and Education Center (ARDEC; 1,524 m). A potential 5 PAP measurements were collected from each bull: 1) Weaning PAP at ARDEC (1,525 m); 2) Yearling PAP at ARDEC; 3) PAP after acclimating for 28 days at Fort Lewis College (FLC; 2,470 m), Hesperus, CO; 4) before returning to ARDEC from FLC after 110 days at FLC; and 5) after re-acclimating for 57 days to the moderate elevation at ARDEC when the bulls were 557 ± 2.92 d

(18 mo) of age. In model development, yearling PAP measurement, elevation, and age were determined to be important ($P < 0.05$) sources of variation. Also, PAP increased ($P < 0.05$) from moderate altitude to high altitude. In Study II (Chapter 4), yearling PAP in the model accounted for more variation in the prediction of the initial high-altitude PAP than it did in the prediction of the subsequent high altitude PAP measurements. Results of this study suggested that the yearling PAP measurement collected at 1,525 m was only a moderate predictor of a PAP measurement collected after 21 days at 2,470 m and these types of predictions weaken after ~ 90 days at high elevation. Overall, Study II (Chapter 4) suggested that as time increased ($p < 0.05$) between the mPAP measures the amount of variation accounted by the initial mPAP measure declined ($p < 0.05$). However, PAP has been considered to be the most accurate indicator of an individual's susceptibility to HAD if is measured at high altitude and near 18 months of age (Holt and Callen 2007). This thesis suggested that yearling PAP measured at moderate elevations was a moderate and short-term indicator of future PAP performance in beef bulls when moving to high altitudes. Yearling PAP measurements are likely less indicative of PAP, the longer bulls reside at high elevation. It should be noted that high-altitude PAP observations will likely have higher correlations and be a stronger indicator to future high-altitude PAP measures. The altitude of the ARDEC facility (1,525 m) of CSU is moderate; therefore, questionable if it yields enough hypoxic stress to determine if a bull has PAP that will be acceptable or unacceptable for lifetime residence in a mountainous beef production system. Breed was not a significant variable in this thesis. This is likely due to limited numbers being evaluated in each breed. To further study breed influence, greater numbers of bulls being analyzed is necessitated. Therefore, this challenge warrants additional research when considering the diversity of beef operations in the Western US.

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CHAPTER I

INTRODUCTION AND OBJECTIVES

1.1 Introduction

There are a multitude of considerations that the beef industry faces related to cattle management. These considerations include illness/disease, resources, consumer preferences, and welfare. Profitability of herds within the beef industry is influenced by the proper management of genetic and environmental influences. Genetic influences are dependent on heritability, parentage, breed, and genetically correlated traits. Environmental influences that affect profitability of a herd include elevation adaptability, season, temperature, maternal environment, and weed or vegetation exposure (Hohenboken et al., 2005). Failure of animals to adapt to environmental influences can negatively impact production levels. Breeding and selection decisions can create more productive and efficient animals in result of their adaptability to these environmental influences and reduce possible detrimental effects on production (Hohenboken et al., 2005).

Genetic selection programs should be implemented that optimize inputs and outputs within the beef industry. To do this, cattle need to be efficient, productive, and yield a desirable end-product. This will improve the profitability of the beef industry and uphold sustainability of cattle production environments (Hohenboken et al., 2005). High Altitude Disease (HAD) has negatively affected beef production systems at high elevations since the 1900's. Cattle that are unable to cope with altitude-induced hypoxia may die from right-side heart failure, which creates economic hardship. This disease has been observed and studied since the early 20th century

(Glover and Newson, 2017), but there has not been a significant decrease in prevalence reported at high elevations (Malherbe et al. 2012; Neary et al., 2013).

Pulmonary Arterial Pressure (PAP) is the best-known indicator trait of an animal's ability to tolerate high altitude hypoxia. This trait and its expected progeny differences (EPD) are currently used to make selection decisions in beef cattle production systems at high elevations. As such, it is important to understand and examine the factors that affect PAP scores and the susceptibility of an animal to HAD. Pulmonary arterial pressure is a measure for pulmonary hypertension (PH) and is the phenotypic measure used to determine an individual's risk to HAD. Yearling animals PAP tested with moderate to high PAP scores (> 41 mmHg) are considered more susceptible to HAD and its complications. Right-sided heart failure that results from the hypoxic conditions at altitudes greater than 1,500 m is a common pathophysiological observation of HAD (Thomas et al., 2018). The amount of increase in PAP scores is directly related to degree of hypertrophy in pulmonary arteries and ventricular workload leading to PH and right-sided heart failure (Holt and Callan, 2007). Previous reports suggested that PAP measurements are moderately heritable, which is important when selecting bulls for high altitude beef production systems (Shirley et al., 2008; Crawford et al.,2016; Pauling et al., 2018; Speidel et al., 2020). Expected progeny differences (EPD) have been calculated to facilitate the selection and usage of bulls regarding their PAP measurements (Speidel et al., 2020). An issue with utilizing PAP as an indicator of an animal's susceptibility to HAD is the accuracy based on the varying altitudes where PAP was collected and age of the individual (Pauling et al., 2018; Speidel et al., 2020). It was suggested that the most accurate testing age for PAP is approximately 18 months at an elevation above 1,524 m (Holt and Callan, 2007). However, given the management of most beef

production systems, PAP measurements are typically collected prior to 16 months of age and often at moderate altitude.

It is pertinent to determine the genetic and environmental facts that effect HAD to attempt to decrease the incidence of this disease. Incidence of HAD is reported to be 3% to 5% in native high-altitude cattle populations. Given the estimated 1.5 million cattle raised at high elevations, this would lead to upwards of 75,000 head predicted to be affected by complication of HAD (Holt & Callan, 2007; Williams et al., 2012; Speidel et al., 2020). Previous research efforts pertaining to HAD and PAP include heritability estimation, genetic correlations between sexes, comparison of affected and unaffected animals, the regression of PAP on age, breed differences within PAP, correlation between moderate and high elevation PAP (Will et al., 1975a; Schimmel and Brinks, 1983; Enns et al., 1992; Cockrum et al., 2014, Crawford et al., 2015; Speidel et al., 2020). There is a lack of research on the repeatability of PAP across elevations, as historically only one PAP measurement is recorded per animal. More knowledge could be achieved in determining if a single PAP measurement is completely indicative of lifetime PAP performance. This will provide better selection and management procedures for producers, especially in a high-altitude location.

The American Angus Association published the first association wide EPD for PAP (Pauling et al., 2018; American Angus Association, 2019). Development of EPD with an acceptable accuracy requires phenotypic information from a sire's progeny. Accuracy of EPD values range from 0 to 1, with values close to 1 being considered closest to the true genetic merit of the animal. Accuracy is a function of the amount of information utilized to calculate the EPD. Due to the need for data in estimation of EPD, PAP information from moderate and low altitude may be necessitated. The AAA evaluated PAP using data from moderate elevations as a correlated

trait to high-elevation PAP EPD (Pauling et al., 2018). This study reported a genetic correlation of 0.83. This was the first study that reported the relationship of PAP among various elevations. Therefore, there is need to learn more about this trait and the many sources of variation (breed, age, altitude, sire, etc.) that may influence breeding value estimations. With EPD for PAP measurement available through a limited amount of breed associations, it is important to determine the implications of the movement of bulls to and (or) from moderate and high elevations.

This thesis' over-arching goals were to determine if lifetime PAP can be determined by a yearling measurement at moderate elevation. This effort also evaluated the impact of movement in altitude, which often happens in Western US beef production systems, on PAP measurements and the relationship between PAP at moderate altitude (1,525 m) to PAP at high altitude (2,470 m). Due to the aforementioned, a specific objective of this thesis was to analyze repeated measures of PAP and determine correlations with measures across time and elevation.

1.2 Objectives

The underlying theme of this thesis was to further examine pulmonary arterial pressure (PAP) and its application to the beef industry. This will be accomplished through three objectives:

1. To explore and estimate correlations between different ages and elevations
2. To determine usefulness of yearling moderate altitude PAP in beef bulls that are transported to high elevation for short- and longer-term management, and
3. To determine usefulness of feedlot entry PAP to additional PAP measures as the cattle approach finishing and harvest.

LITERATURE CITED

American Angus Association. 2019. Research PAP EPD launched by Angus Genetics Inc. Available from https://www.angus.org/Pub/Newsroom/Releases/020119-pap-epd-launch.aspx [accessed June 12, 2021].

Cockrum, R. R., X. Zeng, N. F. Berge, J. M. Neary, F.B. Garry, T. N. Holt, H. D. Blackburn, S. Thomas, S. E. Speidel., D. J. Garrick, R. M. Enns, and M. G. Thomas. 2014. Angus cattle at high altitude: genetic relationships and initial genome wide association analyses of pulmonary arterial pressure. In Proc. 10th World Cong. Genet. Appl. Livest. Prod., Vancouver, British Columbia, Canada.

Crawford, N. F. 2015. Pulmonary arterial pressure as an indicator for high altitude disease in cattle: breed differences and relationships with growth performance. M.S. Thesis. Colorado State University, Fort Collins, Colorado.

Crawford N. F., M. G. Thomas, T. N. Holt, S.E. Speidel, and R. M. Enns. 2016. Heritabilities and genetic correlations of pulmonary arterial pressure and performance traits in Angus cattle at high altitude. J. Anim. Sci. 94:4483-4490.

Enns, R. M., J. Brinks, R. Bourdon, and T. Field. 1992. Heritability of pulmonary arterial pressure in Angus cattle. In Proc. West. Sect. Am. Soc. Anim. Sci. 43:111-112.

Glover, G. H., and I. E. Newsom. 1917. Brisket Disease: Bulletin. No. 204. Colorado Agricultural College, Fort Collins, Colorado.

Hohenboken, W., T. Jenkins, J. Pollak, D. Bullock, and S. Radakovich. 2005. Genetic improvement of beef cattle adaptation in America. In: Proc. 37th Beef Improvement Federation Research Symposium and Annual Meeting. p. 115-120.

Holt, T. N., and R. J. Callan. 2007. Pulmonary arterial pressure testing for high mountain disease in cattle. Vet. Clin. N. Am: Food Anim. Pract. 23:575-596.

Malherbe, C. R., J. Marquard, D. E. Legg, K. M. Cammack, and D. O'Toole. 2012. Right ventricular hypertrophy with heart failure in Holstein heifers at elevation of 1,600 m. J. Vet. Diag. Invest. 24:867-877.

Neary, J. M., D. H. Gould, F. B. Garry, A. P. Knight, D. A. Dargatz, and T. N. Holt. 2013a. An investigation into beef calf mortality on five high altitude ranches that selected sires with low pulmonary arterial pressures for over 20 years. J. Vet. Diag. Invest. 25:210-218.

Neary, J. M. 2013b. Pre-weaned beef calf morality on high altitude ranches in Colorado. M.S. Thesis. Colorado State University, Fort Collins, Colorado.

Pauling, R. C., S. E. Speidel, M. G. Thomas, T. N. Holt, and R. M. Enns. 2018. Evaluation of moderate to high elevation effects on pulmonary arterial pressure measures in Angus cattle1. *J. Anim. Sci*. **96**:3599–3605. doi:10.1093/jas/sky262

Schimmel, J. G., and J. Brinks. 1982. The relationship of pulmonary arterial pressure with postweaning performance traits in yearling beef bulls. In: Proc. West. Sect. Amer. Soc. Anim. Sci. p 203-205.

Shirley, K. L., D. W. Beckman, and D. J. Garrick. 2008. Inheritance of pulmonary arterial pressure in Angus cattle and its correlation with growth. J. Anim. Sci. 86:815-819.

Speidel, S.E., M.G. Thomas, T.N. Holt, R.M. Enns, Evaluation of the sensitivity of pulmonary arterial pressure to elevation using a reaction norm model in Angus Cattle, J. Anim. Sci. Volume 98, Issue 5, May 2020, skaa129, https://doi.org/10.1093/jas/skaa129

Thomas M.G., J.M. Neary, G.M. Krafsur, T.N. Holt, R.M. Enns, S.E. Speidel, F.B. Garry, A. Canovas, J.F. Medrano, R.D. Brown, and K.R. Stenmark. 2018. Pulmonary hypertension in beef cattle: a complicated threat to health and productivity in multiple beef industry segments. White Paper for Certified Angus Beef. http://www.cabpartners.com/news/research.php. Accepted 5/9/2018.

Will, D. H., J. L. Hicks, C. Card, and A. Alexander. 1975a. Inherited susceptibility of cattle to high-altitude pulmonary hypertension. J. Appl. Physiol. 38:491-494.

CHAPTER II

LITERATURE REVIEW

2.1 Introduction

Genetic selection programs should be implemented that optimize inputs within the beef industry. To do this, cattle need to be efficient, productive, and yield a desirable end-product. This will improve the profitability of the beef industry and uphold sustainability of cattle production environments (Hohenboken et al., 2005). High Altitude Disease (HAD) has negatively affected beef production systems at high elevations since the 1800's. Cattle that are unable to cope with altitude-induced hypoxia may die from right-side heart failure, which creates economic hardship.

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Speidel et al., 2020). It was suggested that the most accurate testing age for PAP is approximately 18 months at an elevation above 1,524 m (Holt and Callan, 2007). However, given the management of most beef production systems, PAP measurements are typically collected prior to 16 months of age and often at moderate altitude.

The American Angus Association published the first association wide EPD for PAP (Pauling et al., 2018; American Angus Association, 2019). Development of EPD with an acceptable accuracy requires phenotypic information from a sire's progeny. Due to the need for data in estimation of EPD, PAP information from moderate and low altitude may be necessitated. The AAA evaluated PAP using data from moderate elevations as a correlated trait to high-elevation PAP EPD (Pauling et al., 2018). This study reported a genetic correlation of 0.83. This was the first study that reported the relationship of PAP at various elevations. Therefore, there is need to learn more about this trait and the many sources of variation (breed, age, altitude, sire, etc.) that may influence breeding value estimations. With EPD for PAP measurement becoming available through breed associations, it is important to determine the implications of low to moderate elevation PAP measurements on overall usefulness in estimating high altitude PAP EPD and for the movement of bulls to and (or) from moderate and high elevations.

2.2 Environmental Challenges and Genetic Contributions to Adaptability

A key role in the success of high-altitude beef production systems is the ability of cattle to adapt and perform. Physical, chemical, biological, and environmental factors occur and affect the physiological reactions animals have to a particular environment. Understanding environmental limitations of animals and what will make an optimal environment is of increasing importance (Johnson and Vanjonack, 1976). The adaptability of cattle is a key to sustaining beef cattle

production systems in harsh environments. This is evidenced by the potential benefits of: enhanced animal well-being, enhanced conservation of resources/forage utilization, increased profitability, and an increase in the desirability of beef products for consumers (Hohenboken et al., 2005; Nardone et al., 2010).

2.2.1 General Environmental Challenges Affecting Cattle

Identifying prominent stressors, environmental challenges, genetic variation and covariation of adaptive and production traits, and identifying indicator traits essential to adaptation are keys to achieving genetic improvement of adaptation in beef cattle of America (Hohenboken et al. 2005). Management practices provide the tools to overcome some environmental obstacles or lessen the impact severity on animals. Environmental obstacles that hinder cattle adaptability to their surroundings: season, weeds, vegetation exposure, management practices, elevation, and oxygen availability.

A phenotypic response developed by an animal to a single source of environmental stress can be defined as acclimation (Fregly, 2011). Production levels, morbidity, and mortality are affected by climate and season, and are considered vital in the determination of cattle adaptability. Weather factors like temperature, atmospheric pressure, and precipitation can hinder cattle adaptability to a region. A challenge within beef production systems is a lack of control on environmental factors, especially compared to dairy, swine, and poultry production industries. In general, beef cattle are reared outdoors in contrast with the aforementioned production systems. This leaves beef cattle exposed and vulnerable to potentially extreme environmental conditions. Cattle undergo changes in physiological functions when attempting to acclimate and overcome environmental challenges. They may experience reduced feed intake, altered production and

reproductive efficiency, and reduced health related physiological functions (Beede and Collier, 1986; Lacetera et al., 2006).

Ingestion of certain vegetation can contribute to environmental adaptability of cattle (Pendlum et al., 1980). Ingestion of tall fescue (*Festuca arundinacea*), for example, can cause fescue toxicosis. Fescue toxicosis is associated with ingestion of tall fescue infected with an endophyte, this results in heat intolerance, excessive salivation, reduced feed consumption (leading to reduced gains), reduced milk production, and elevated body temperature (Stuedemann and Hoveland, 1988). Effective management and selection of cattle for such an environment, rich in fescue, can play a role in the success and susceptibility of an animal to disease. Selection of breeding stock cattle suited for an environment and tolerant to specific environmental challenges allows for the genetic improvement of those animals, this will ultimately decrease susceptibility within the given environment.

2.2.2 Genotype by Environment Interaction

Genetics of an animal and (or) herd likely contributes to adaptability. Genetics and environment often interact, which is knowns as genotype by environment interaction. In genotype by environment interaction, the differences observed or measured in performance between two or more genotypes changes from one environment to another (Bourdon, 1999). In the previously discussed fescue toxicosis there are animals that are susceptible to the poisoning and others that are resistant in differing environments (i.e. environments containing infected fescue versus uninfected fescue), which is an example of genotype by environment interaction. The performance of these animals has a potential for re-ranking when moved from one environment to another.

Another example of genotype by environment interaction is changes in elevation. Changes in elevation can affect how cattle adapt to reduced environmental oxygen. Hypoxia is a condition in which the body is deprived of adequate oxygen. Hypoxic environments can elicit and unfavorable response of the pulmonary system. It is understood that there is a genotype by environment interaction occurring in HAD. This is evidenced by the fact that not all animals residing at high altitude develop HAD. Animal susceptibility to HAD is indicated by PAP scores, this will be discussed more in depth in subsequence sections. There is speculation that animals with high low elevation PAP scores will have even higher PAP scores at high altitudes. It has not been researched whether animals with low PAP scores at low altitude will also have low PAP scores at high altitude. The potential for re-ranking in these animals when changing environments between low and high altitude indicates the genotype by environment interaction. However, there may be other environmental influences into the onset of HAD in cattle.

2.3 High Altitude Disease

High altitude disease, alternatively termed high mountain disease and brisket disease, has been reported in beef cattle since 1889 (Glover and Newsom, 1917). The disease usually presents in a noticeable accumulation of edematous fluid, particularly between forelegs/neck (brisket) and along the lower thoracic and abdominal cavity. Increased vascular hydrostatic pressure and subsequent loss of fluid into extravascular spaces causes this fluid accumulation (Holt and Callan, 2007). Exhaustion of the heart muscle associated with a varying degree of dilation and hypertrophy is presented as the cause of HAD by initial research (Glover and Newson, 1917). The occurrence of pulmonary arterial hypertension (PAH) causes HAD; however, they are not the same thing. High altitude disease is an animal model of hypoxic pulmonary hypertension and

may represent a naturally occurring experimental model for heart failure in cattle (Kuida et al., 1963; Newman et al., 2011).

2.3.1 Pulmonary Arterial Hypertension

Beef cattle have a low gaseous exchange capacity relative to their basal oxygen need in comparison to other mammals (Veit and Farrel, 1978). Cattle have mainly been selected to improve feedlot and various production traits. Modern cattle have small lungs in relation to their body size, making them susceptible to cardiopulmonary disease (Neary et al. 2013a). Pulmonary arterial hypertension originates in the pulmonary arteries of the lungs in an animal and is characterized by the narrowing of the pulmonary vasculature due to increased size of the arterial adventitia leading to a progressive increase in pulmonary vascular resistance, and consequently increasing right ventricle load causing failure of the right ventricle (Humbert et al., 2004).

Pulmonary arterial hypertension is also referred to as simply "pulmonary hypertension (PH)." Vascular changes in pulmonary hypertension include vasoconstriction, smooth-muscle cell and endothelial-cell proliferation of the adventitia, and thrombosis (Farber and Loscalzo, 2004). "Cor pulmonale" is a term used to describe the collective conditions of right heart dilation, hypertrophy, and following failure caused by pulmonary hypertension and pulmonary vascular resistance (Peek and McGuirk, 2008). The causes of the illness in cattle are the counterpart of pulmonary hypertensive heart disease in humans (Hecht, 1956).

2.3.2 Right Heart Failure (RHF)

When left unmanaged, PAH can lead to RHF and death; and, at this time, there is not a treatment. During hypoxic conditions, such as high elevation, a morphologic change can be

observed in the small pulmonary arteries and arterioles which causes and increase in resistance to normal blood flow (LeValley, 1978). Cattle are more susceptible to hypoxic pulmonary vasoconstriction due to their unusually muscular pulmonary vasculature which may ultimately lead to RHF (Heath et al., 1984).

2.3.3 Mechanism of Pulmonary Hypertension and Vascular Changes

Pulmonary arterial hypertension has multifactorial pathophysiology. All cases and forms of PAH cannot be explained by one factor or gene (Humbert et al., 2004). It is hypothesized that PH involves two process that are related: 1. progressive increase in arterial vasoconstriction due in part to vascular smooth muscle hypertrophy, and 2. obstruction of pulmonary arteries (Grover et al., 1963). Pulmonary hypertension in HAD animals is a result from exaggerated pulmonary vasoconstriction due to hypoxic conditions (Kuida et al., 1963). Pulmonary hypertension in cattle appeared to be a result of increased resistance of blood flow through the lungs. The reduction in cross-sectional area of pulmonary vasculature supported this (Will et al., 1962; Kuida et al., 1963).

Figure **2.1** represents the stiffening, impedance, and resistance associated with PH (Neary, 2013). This image complements previous research efforts by Elzinga and Westerhof (1973), Zuckerman et al. (1992), and Stenmark et al. (1987, 2009). Farber and Loscalzo (2004) stated that there are three mechanisms for developing PAH in humans: hypoxia, anorexigens, and central nervous system stimulants. Alexander et al. (1960) postulated that the PH response in cattle could be due to chronic hypoxia. A strong relationship between pulmonary pressure response under acute and chronic hypoxia brought evidence to this postulation (Will et al.,

1975b). This suggested that acute and chronic hypoxia likely share a common mechanism in cattle.

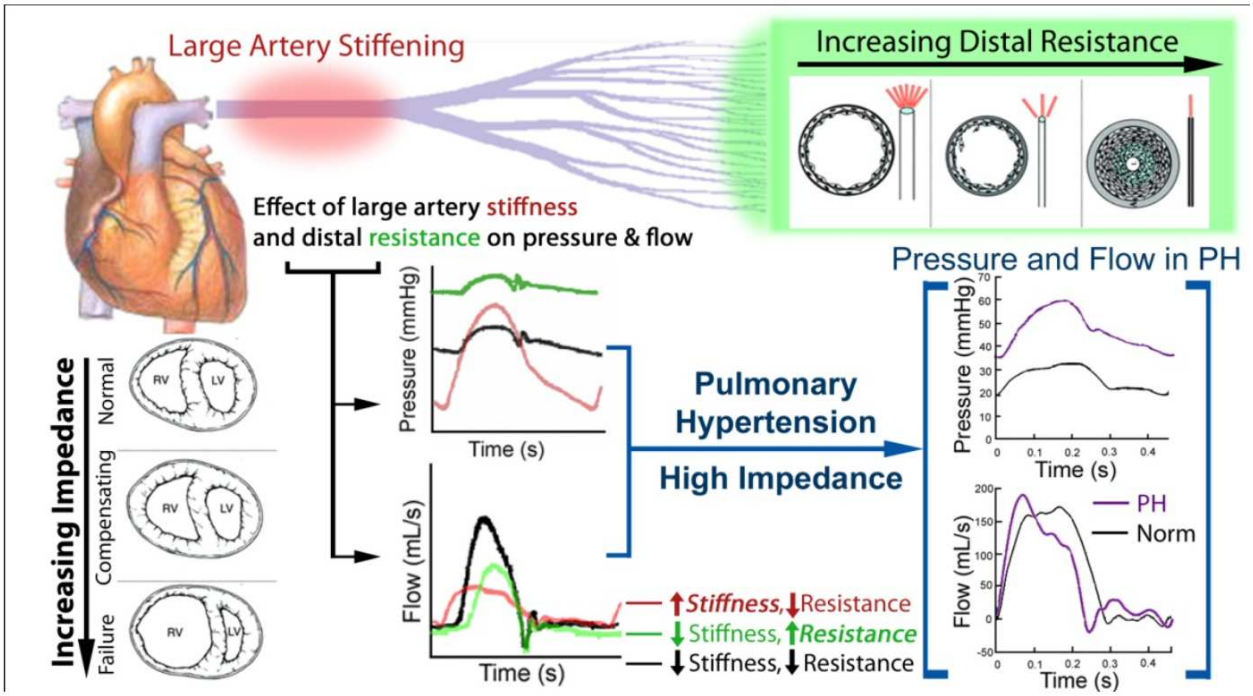

Figure 2.1 Diagram illustrating the relationship between ventricular work, flow impedance due to pulmonary artery stiffening, and resistance to flow due to narrowing of distal pulmonary vessels. Vascular stiffness determines the overall hemodynamic changes associated with pulmonary hypertension. Structure function changes in vessel wall elastin and distal resistance due to medial hypertrophy do not act independently but form a coupled system to determine vascular stiffness. (Neary, 2013)

Previous studies have examined pulmonary arterial vessel structural changes and the effect on presence and (or) persistence of PH in cattle located at high altitude (Jaenke and Alexander, 1973; Tucker and Rhodes, 2001; Stenmark et al., 2006). The findings from these previous studies suggested that chronic hypoxic conditions influence thickening of the adventitia and an increase in the diameter of pulmonary vessels (Reeves and Leathers, 1967; Stenmark et al., 1987). This structural remodeling contributes to right ventricular workload and alters flow dynamics which can result in pulmonary hypertension (Neary et al., 2013). There is a strong correlation between the amount of medial smooth muscle in small pulmonary arteries and

magnitude of PH in response to hypoxia (Tucker et al., 1975). Cardiac ventricular ratios from that study showed significant ventricular hypertrophy in the animals at high altitude. Jaenke and Alexander (1973) related structural changes in the pulmonary system to a progressive increase in PAP in calves exposed to high altitude. Tucker and Rhodes (2001) concluded that young calves were the most responsive to high altitude and that cattle with thick-walled pulmonary arteries are high altitude hyper-responders. Collateral ventilation is the ventilation of alveolar structures through passages or channels that bypass the normal airways (Fessler, 2005). There is a correlation between the absence of collateral ventilation and the presence of thick-walled pulmonary arteries in cattle. Kuriyama and Wagner (1981) concluded that due to the lack of collateral ventilation in cattle, that their vessel walls were thick at low altitude and even thicker at high altitudes, this increases the development of high altitude pulmonary hypertension.

Rhodes (2005) stated that a degree of variability can be seen in the magnitude of pulmonary hypertension and degree of right ventricular hypertrophy in mammalian species and individuals within a species when stimulated under similar conditions. Implementation of selective breeding strategies can by utilized by beef cattle producers to attempt to decrease susceptibility of cattle to HAD. Due to increased genetic selection for production traits, beef cattle have small lungs relative to their body size and metabolic demand (Neary et al., 2013). This may increase their risk of cardiopulmonary disease. However, it should be noted that cattle utilized in the study by Neary et al. (2013) were primarily for growth and market performance. Analysis and comparison of different populations of cattle, e.g. fertility focused, would be necessary for a more complete support of that statement. Pathogenesis of bovine PH still has more areas to study.

2.3.4 Pulmonary Hypertension within High Altitude Disease

2.3.4.1 Environmental Challenges with HAD

Conditions that may induce HAD/hypoxia include exposure to high altitude, respiratory impairment secondary to chest wall abnormalities, airway obstruction, pneumonia, pulmonary edema, emphysema, or pulmonary vascular disease (Angel and Tyler, 1992).

2.3.4.1.1 Weeds and Vegetation

Calves at high elevation and exposed to swainsonine, a compound contained in locoweed (*Astragalus* and *Oxytropis*), may be at increased risk of development of HAD (Panter et al., 1988; Holt and Callan, 2007). Calves fed locoweed at high altitude (3,090 m) had microscopic lesions suggestive of HAD and demonstrated clinical signs of HAD (James et al., 1991). It is possible that the effect of swainsonine exposure on HAD development is due to cardiotoxic effects especially in combination with hypoxic pulmonary hypertension, however there is no specific data indicating swainsonine elevates PAP scores and causes PH.

2.3.4.1.2 Climate and Season

A study by Jensen et al. (1976) found that HAD accounted for 5.8% of the 1,988 feedlot cattle necropsied. Jensen et al. (1976) described that HAD occurred in all seasons but was the most common during fall and winter. Environmental cold caused an increase in PAP and vascular resistance and a decrease in arterial oxygen tension (Will et al., 1978). PAP scores increased upon exposure to temperatures that ranged between 0°C and 5°C. The major contributing factor to the increase in PAP the increased pulmonary flow during the first 24 h of cold exposure. Hereford calves in a controlled temperature setting (14°C to 16°C) were

compared to calves in cold temperature settings (-2°C to 1°C) had lower PAP scores ($P < 0.05$). One degree decrease in difference was associated with a 1.38 mm Hg increase in PAP (Busch et al., 1985). The study concluded that mild exposure to cold temperatures causes pulmonary hypertension in normal cattle. Altitude was found to have an additive effect to cold temperature response of PAP scores. Cold exposure alone increased PAP scores, but addition of high-altitude exposure increase PAP above cold exposure alone (Busch et al., 1985).

2.3.4.1.3 Elevation and Oxygen Availability

Oxygen availability and elevation can affect the effectiveness of cattle to environmentally adapt. Pulmonary arterial pressure scores have been found to increase 1 to 2 mm Hg for every 304.8 m increase in elevation (Holt and Callan, 2007). Increasing residence altitudes increased PAP scores; however, the magnitude of PAP changes was less in native cattle than cattle produced in low altitude production systems (Will et al., 1975).

Will et al. (1962) administered oxygen to evaluate reaction at altitude. The study at altitude (3,048 m) administered 100% oxygen to yearling Hereford steers for 10 minutes. The study found an immediate fall in mPAP. However, after removal of oxygen, pressures increase to baseline PAP measurements prior to the oxygen administration. This showed that administration of oxygen can alter reaction to altitude changes, however it must be continuously administered for ongoing effect. Alexander et al. (1960) performed a similar study to two hypertensive cattle. A reduction of PAP was evaluated. Prolonged oxygen administration can resolve PH, even if emphysema or bronchitis is present causing a hypoxic environment (Angel and Tyler, 1992).

Adaptation of animals in a specific environment declines when non-native animals are used for breeding purposes (Hohenboken et al., 2005). This is due to the disruption of gene

combinations and allele frequencies favorable to production in that environment (Hohenboken et al., 2005). This may explain the differing responses to hypoxia in cattle. This also may allude to a genetic relationship. Breeding to outside sires may not adequately suit high altitude production environments.

2.3.5 Role of Genetics and Selection in HAD

Pulmonary arterial pressure scores have been estimated to be moderate to highly heritable (0.20 to 0.46) and can be used to predict HAD or PH susceptibility and to make selection decisions (LeValley, 1978; Enns et al., 1992; Cockrum et al., 2014, Crawford et al., 2015). The susceptibility of cattle to PH and HAD is presumed to be partially genetically controlled (Will et al., 1975a).

Pulmonary hypertension has a multifactorial pathophysiology and PAP is a polygenic trait; not all information about these is completely understood (Humbert et al., 2004; Cockrum et al., 2014). Candidate genes have been (are being) identified to provide greater insight into the pathogenesis of HAD. Newman et al. (2011, 2015) discovered 5 potential genes possibly involved in PH: NADH dehydrogenase (ubiquinone) flavoprotein 2 (NDUFV), myosin heavy chain 15 (MYH15), myocardial signaling protein (FKBP1A), and endothelial PAS domain-containing protein 1 (EPAS1). Examination of the expression of these genes can identify disease processes, and physiological, cellular, and molecular functions.

2.3.6 Signs and Symptoms of HAD

HAD is commonly noticed by swelling/edema in the brisket and abdominal region of the animal, therefore the disease was termed brisket disease. Edema is caused by increased

hydrostatic pressure due to stiffening of vessels in the cardiopulmonary system leading to right ventricle cardiac failure and venous hypertension (Holt and Callan, 2007)

Table **2.1** describes clinal signs and symptoms associated with HAD in cattle (Glover and Newsom, 1917; Holt and Callan, 2007; Neary et al., 2013; Crawford et al., 2015). Typical course of HAD lasts between two weeks and three months; most cattle dying within a month after noticeable symptoms (Glover and Newsom, 1917). Pierson and Jensen (1956) stated that the progression of the disease lasts between one and twelve weeks.

Table 2.1 Antemortem and postmortem signs and symptoms associated with high altitude disease (HAD) in cattle.[i]

Antemortem	Postmortem
Lethargy	Increase hepatic enzymes
Tachypnea (rapid breathing)	Enlarged, hard liver
Drooped ears	Enlarged, dilated heart
Rough hair coat	Lesions
Ataxia (lack of muscle control)	
Jugular vein distention	
Brisket edema	
Exophthalmia (protrusion of eyeballs)	
Ascites (fluid in abdomen)	
Generalized edema: -intermandibular, ventral abdominal, limb	
Decreased appetite	
Recumbent (lying down, inactive)	
Unable to rise	
Elevated heart and respiratory rates	
Muffled heart sounds	
Diarrhea	
Moist, sporadic cough	
Gradual emaciation	
Inflammation	

[i] Compiled from research by Glover and Newsom (1917), Holt and Callan (2007), and Neary et al. (2013)

2.3.7 Impact of HAD on Beef Industry

2.3.7.1 Prevalence of HAD

High altitude beef production systems produce approximately 1.5 million calves per year. With HAD having an incidence rate of 3-5%, complications from this disease would result in more than 75,000 animals affected per year (Holt and Callan, 2007; Williams et al., 2012). Holt and Callan (2007) reported an example where a Colorado ranch experienced an approximate 25% loss in yearling cattle in a single year. Even though cattle at high elevation comprise a fairly small percentage of total US beef cattle numbers, PH can have a massive impact on high elevation producers.

Cattle are thought to be predisposed to HAD with occurrence dependent on a multitude of factors. Will et al. (1975a) examined differences in PAP over 2 generations of calves from susceptible and resistant parents. Susceptible calves (those born from susceptible parents) at 10 days of age had higher PAP at 1,524 m and 4,572 m than the resistant calves 9those born from resistant parents). At 90 days of age, during acute hypoxic conditions (4,572 m; artificially created in a hypobaric chamber), susceptible calved tended to have higher PAP scores than that of the resistant calves. At an elevation of 3,048, at 124 days of age, all susceptible calves developed signs of heart failure (Will et al., 1975a). None of the resistant calves developed these signs. These results agreed with results from Glover and Newson (1917), as they determined that calves sired by low altitude bulls were more susceptible than calves sired by native bulls.

Neary et al. (2013a) reported in a survey of 5 ranches, that half of the total necropsied calves (n = 28) between 6 weeks and 7 months of age had lesions associated with PH and the other half had lesions associated with pneumonia. The ranches in question had been utilizing a low PAP selection process for their bulls for approximately 20 years, and yet still half of the death loss was due to RHF secondary to PH. Neary stated that this may be due to the fact that

PAP measurements and screening cannot eliminate the occurrence of PH if the disease is not solely attributed to alveolar hypoxia.

Recently, brisket disease as a result of PH has been observed in feedlot cattle. The initial report in feedlot cattle was located at 1,600m (Jensen et al., 1976). In this study, 116 out of 1,988 animals necropsied had suffered from RHF secondary to PH. Jensen proposed the occurrence of PH in feedlot cattle could be caused by genetic susceptibility, mountainous origins, rapid growth, and (or) hypoventilation. Feedlot cattle were gaining between 1 and 1.5 kg a day at the time of the study. This led the authors to postulate that there may be a correlation between rapid growth rates and a drastic increase in the bovine cardiopulmonary system output. Hypoventilation caused by intra-abdominal pressure was proposed by the authors to result in airway hypoxia and heart failure. Fifty animals within the study developed brisket disease and showed signs of pneumonia which could contribute to airway hypoxia.

The second leading cause of death in a study on Holstein heifers at a Colorado dairy at an elevation of 1,600m was RHF secondary to right ventricular hypertrophy (Malherbe et al., 2012). Death loss at the dairy due to RHF accounted for 22% of total heifer deaths over a 7-year period. Ten heifers were determined to have been affected by RHF as reported in the clinical details. Seven of the 10 heifers lost had been treated for pneumonia prior to death.

Congestive heart failure has been problematic in late stage finishing of feedlot cattle. This may be due to a high mean PAP during the feeding period (Neary et al. 2015). PAP observations were collected on a group of male calves, ranging from 4 to 18 months of age, to evaluate the authors' hypothesis. The calves were born and raised at an average elevation of 2,170 m. After weaning, calves were then moved to a lower elevation. Animals were PAP tested 4 times between the ages of 4 to 18 months of age. Two of the PAP observations were at low elevation

(1,560 m or 1,300 m) and the other two PAP observations were at high elevation (2,170 m). Mean PAP observations increased through the feeding period. Calves with the highest PAP observations at high elevation also had the highest PAP observations through the feed test period. The increased mean PAP through the feed test could be amplified by body fat accumulation and ruminal engorgement associated with the finishing stages of feedlot cattle (Jensen et al. 1976). The ruminal engorgement can increase the intra-abdominal pressure as previously stated, thus preventing the animal from full lung capacity utilization leading to hypoxia induced PH. Neary stated that the body fat accumulation may cause a predisposition to higher systolic PAP and arteriolar wedge pressure, contributing to increased mean PAP and cardiac dysfunction.

2.3.7.2 Economic Impact of HAD/Economic Relevance of Genetic Improvement for a Health Trait

In high altitude producing regions, PAP is a large factor taken into consideration during purchase. In a study on a herd produced at high altitude and for low PAP scores, PAP was shown to have an important influence on sale price (Kessler et al., 2013). High Altitude producers are more willing to pay a premium for lower PAP scores.

The National Animal Health Monitoring System reported from 1986 to 1988 that the cost of deaths of diseased animals was the largest contributor to the total mean annual cost of disease incidence in Colorado cow-calf hers (Salman et al., 1991b). One of the primary causes of morbidity and mortality in cattle raised at high altitude was HAD, accounting for significant losses in growth and reproductive performance (Holt and Callan, 2007). Economically, effects of PH/HAD directly impacts the beef industry. As previously stated, Holt and Callan (2007)

reported death losses up to approximately 5% in cattle residing at high elevation. This translates to a 75,000 head and $60 million annual loss (Williams et al., 2012). Additionally, McCormick (2011) reported estimates of 25 to 40% PH death loss in cattle that were relocated from lower to higher elevations.

The EPD for PAP was initially developed using Tybar Ranch in Carbondale, CO (1,880 m) and CSU Beef Improvement Center in Saratoga, WY (2,170 m) data and has been utilized as a selection tool of varying degrees since the development (Enns et al., 2011). Selection decisions and utilization of the PAP EPD led to a favorable decrease in average PAP EPD values for each respective herd as illustratred by Figure **2.2**.

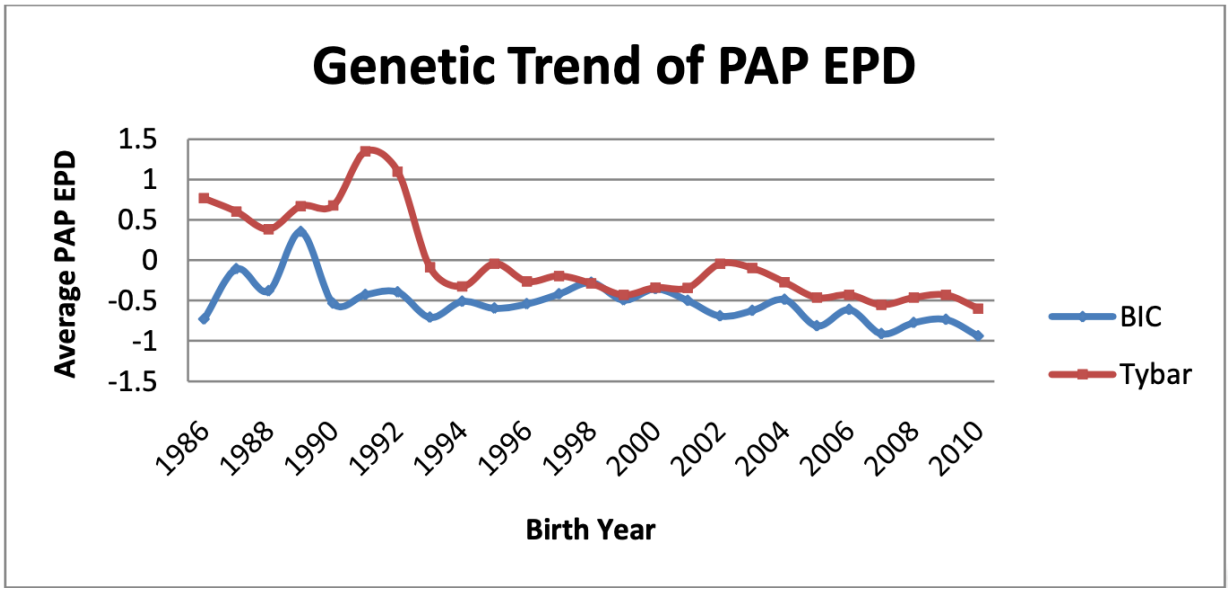

Figure 2.2: Genetic trend in pulmonary artery pressure at the Tybar Ranch (Tybar) and the Colorado State University Beef Improvement Center (CSU-BIC) since selection with EPD began in 1992 (Tybar) and 2002 (CSU-BIC) (Enns et al., 2011).

2.3.8 Management Practices for Avoiding HAD

Currently, there is no known cure for HAD in cattle. Treatment options may mitigate or decrease the severity of HAD on cattle. Treatment of cattle suffering from this disease includes administration of diuretics to decrease cardiac overload, antibiotics for secondary infections, B-

vitamins, and oxygen therapy. Restrictions on water and salt intake and draining of fluid from the thoracic cavity of the chest are other available treatment options (Tim Holt; Crawford et al., 2015). Usage of bulls for breeding purposes raised at altitudes above 2,438 m is recommended as a preventative measure (Glover and Newsom, 1917). Care should be taken in handling during their first weeks of arrival at high altitude to prevent extreme exertion and lessen the extent of exertion (Glover and Newsom, 1917).

2.4 Pulmonary Arterial Pressure (PAP): Scores, Genetics, Influences

2.4.1 Background and History

Pulmonary arterial pressure testing is a method used to confirm the presence of PH (Holt and Callan, 2007). According to Holt and Callan (2007) animals with a PAP observation greater than 49 mmHg should be considered high-risk candidates and not retained as breeding animals for herds located at altitudes greater than 1,524 m. Table **2.2** illustrates different classifications of PAP observations and the interpretation of those classifications.

Until EPD were recently published, PAP testing was the best tool to assist in the selection of cattle less susceptible to PH. Producers have utilized PAP tests for over 40 years. However, even with selection, there are still some herds at higher elevations with death loss caused by PH and RHF. Neary et al. speculated that PAP measurement and screening can't by itself eliminate PH if the disease is not solely attributable to alveolar hypoxia.

Table 2.2: Evaluation of pulmonary arterial pressure scores [1]

PAP	Interpretation
30-35 mmHg	This score is considered excellent and highly reliable.
36-39 mmHg	This score is considered excellent for any animal over the age of 12 months. If the animal is less than 12 months of age, the score is still fairly reliable, but retesting before breeding is suggested
<41 mmHg	Scores less than 41 mmHg are reliable measurements in all animals more than 12 months of age. It is recommended that yearling cattle have a PAP measurement less than 31 mmHg (depending on altitude of the test). The variation in scores 41 mmHg and above is inconsistent and difficult to predict in some cattle as they age. Any animal measuring 41 mmHg and greater should always be retested before use.
41-45 mmHg	This range is acceptable for older animals (i.e., more than 16 months of age). Animals less than 16 months scoring in this range should be retested to predict the future PAP of the animal accurately.
45-48 mmHg	This range is acceptable only for older animals that have been in high elevations for an extended period of time. Animals with this score are more susceptible to environmental stresses leading to HMD and should be considered at some risk. Elevation of test site and where the animal lives must be evaluated closely for those in this PAP score range.
>49 mmHg	Animals that score in this range must always be considered high-risk candidates for developing HMD, not only for themselves but also their offspring. Many animals that have scored in this range have died of HMD. An option for these animals is to move them to a lower elevation for use there. It is also recommended that offspring of these animals never return to high altitude

[1] These figures are based on cattle tested at or above 1800 m at 12 months of age or greater (Holt and Callan, 2007).

2.4.2 PAP Collection Procedure

PAP collection involves passing a flexible catheter through a large bore needle that was placed into the jugular vein. The animal must be properly restrained with head and neck movement restricted due to the invasive nature of the procedure. After restraint, the catheter is passed through the needle, into the jugular vein, passed through the right atrium, through the right ventricle and into the pulmonary artery. A pressure transducer located on the end of the catheter measures systolic and diastolic pressures, which are used to calculate a mean PAP measurement. A veterinarian trained in this procedure will monitor pressure changes and

characteristics that are displayed on the monitor to determine location of catheter in the cardiovascular system. Blood pressure in cattle is typically between 6 and 12 mmHg in the jugular and right atrium, 18 to 30 mmHg in the right ventricle, and 34 to 44 mmHg in the pulmonary artery (Holt and Callan, 2007). Figure **2.3** illustrates changes in blood pressure wave characteristics as the catheter moves through the cardiovascular system.

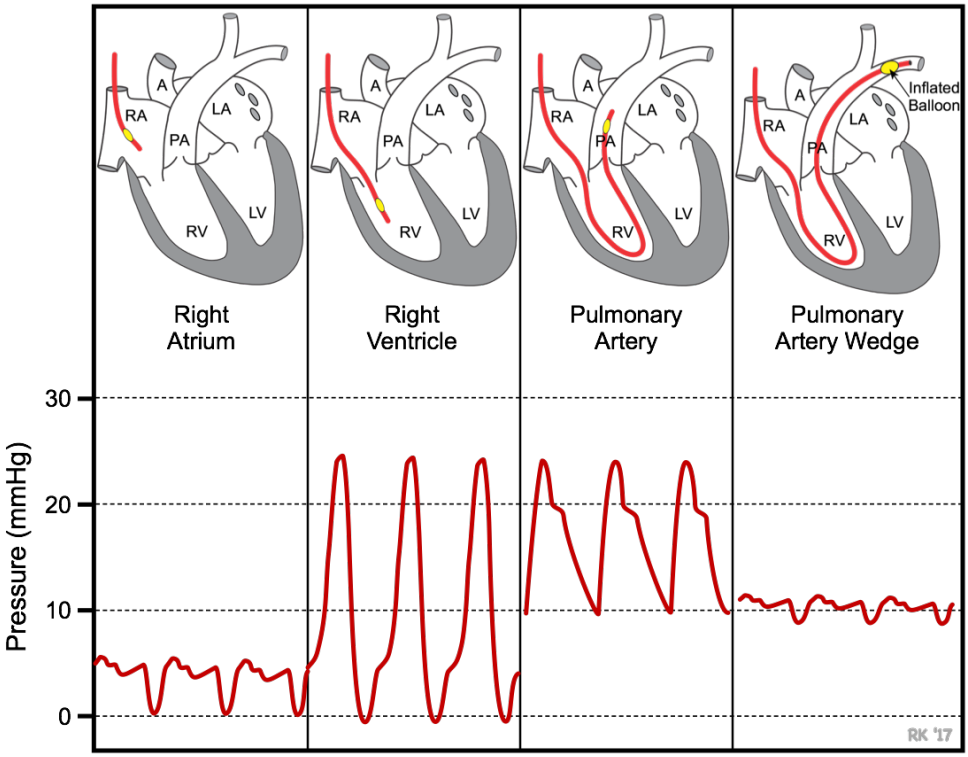

Figure 2.3: A diagram that shows the waveforms as the catheter passes through the right atrium (RA), right ventricle (RV), pulmonary artery, and pulmonary artery wedge. (https://cvphysiology.com/Heart%20Failure/HF008)

2.4.2.1 Alternatives to PAP Testing

As aforementioned, PAP testing is invasive, and it can be costly and time consuming for producers. Producers at lower elevations often do not utilize PAP within their herds due to the fact they are not as commonly affected by PH. Tests at low elevations also are not as accurate in the prediction of animal susceptibility to PH. Ahola et al. (2006) attempted to identify alternatives based on ease of collection and cost effectiveness. The objective was to determine if

there was a relationship between PAP observations and blood components. The blood components were obtained from 3 blood evaluation technologies: pulse oximetry, portable clinical analyzer, and hemogram. Blood components that were evaluated by portable clinical analyzer and hemogram. Pack cell volume (PCV), hemoglobin concentration (HgB), red blood cell count, mean cell volume, mean cell hemoglobin concentration, red cell distribution width (RDW), nucleated cells, platelet counts, mean corpuscular hemoglobin, and mean platelet volume were analyzed with the hemogram. Blood oxygen levels were also evaluated using pulse oximetry. The Pearson correlation coefficients showed moderate correlations between PAP and PCV, HgB, and RDW. Hemogram factors to be included in the multiple regression analysis were determined by utilizing a stepwise model selection approach. Hemoglobin concentration and RDW used in the multiple regression analysis accounted for approximately 31% ($R^2 = 0.305$) of the variability in PAP observations. As such, PAP testing is still considered the best option available to producers for determining an animal's susceptibility to developing PH.

2.4.3 Genetics Associated with PAP

There are only small amounts of studies available in literature that evaluate hypoxia-induced PH from a molecular genetic standpoint in cattle. Newman et al. (2011) described a study using DNA and RNA samples from 20 Angus cattle raised at an elevation of 2,590 m. Fifty percent of these animals were considered normal and the other were considered hypertensive. The study utilized a SNP array in a genome-wide association study to identify gene differences among the two types of cattle identified (hypertensive and normal). From the array, 3 genes were identified: FK Binding protein 1a (FKBP1A), myosin heavy chain 15 (MYH15), and NADH dehydrogenase flavoprotein 2 (NDUFV2). A follow up study completed an analysis of

the evaluation of the previously mentioned genes with PAP (Neary et al., 2014). Angus bulls residing at 2,182 m were sampled. The study concluded that there was a significant association between a T allele variant within the MYH15 gene and low PAP observations in cattle. A small group of Yaks residing at 1,500 m were also sampled, and all were homozygous for the same T allele of the MYH15 gene. Yaks are in the same family as cattle and are better adapted to high altitudes. This is likely due to natural selection of the generations within the mountainous regions of Asia. The association between hypoxic disease and T allele polymorphism suggested that the alleles of MYH15 gene are differentially regulated by hypoxia. However, there is very limited data, and as such a complete causation/correlation cannot be assumed. More genotype analysis with greater data is necessitated.

Neary (2014) tried to identify chromosomal regions associated with PAP and other mean PAP-associated traits in calves. Seven SNP were associated with mean PAP in animals at 4 months of age. These SNP were associated with susceptibility to myocardial/infectious disease and cellular proliferation. There was an association between two SNP and systolic PAP at 6 months of age. One of the aforementioned SNP was located in a region that could indicate that there is a role of hemostasis in susceptibility to PH determination.

Newman et al. (2015) evaluated the Endothelial PAS domain-containing protein 1 (EPAS1) gene. Angus bulls were sampled from 3 different ranches. Of the 41 bulls, 20 were considered hypertensive in their PAP measurements; the other 21 were considered normal. EPAS1 gene has two variants located on exon 12 associated with high altitude PH. The two variants have not been reported in other high altitude tolerant species of animals such as yak and sheep. However, genotyping results from Crawford et al. (2016) suggested that EPAS1 gene may not be effective to distinguish high PAP and low PAP animals. The result indicated that EPAS 1

gene was not a significant predictor in mean PAP scores. The contrast of these studies may be due to small samples sizes and (or) a difference in sample populations, particularly Angus cattle.

2.4.4 Factors Influencing PAP Scores

Cattle displaying signs of PH typically have PAP values > 48 mm Hg (Holt and Callan, 2007). Normal animals at > 1,524 m should have mean central venous pressure of 6 to 12 mm Hg, mean right ventricular pressure of 18 to 30 mm Hg, and mPAP between 34 to 44 mm Hg (Holt and Callan, 2007). Breed, sex, age, pregnancy status, body condition, concurrent illness, environmental conditions, elevation, and genetics can affect PAP scores in cattle (Holt and Callan, 2007). These factors must be considered to accurately use and understand PAP scores

2.4.4.1 Breed

There are incidences of high PAP values in nearly every breed of cattle that has PAP observations, as reported by Holt and Callan (2007). This shows there is no specific breed that completely resistant to effects of hypoxia and PH. Crawford et al. (2015) evaluated breed differences of PAP in more than 2000 bulls at the 4-Corners Bull Test (Hesperus, CO) within the year range of 1983 and 2005. Overall, it was found that in this bull test, Angus-Gelbvieh crossed cattle had the lowest mean PAP. Simmental cattle had the highest mean PAP, in comparison. The breeds included in the dataset were Angus, Charolais, Gelbvieh, Hereford, Limousin, Maine Anjou, Red Angus, Simmental, and Saler bulls. However, the number of cattle within a breed in this study was dependent on those tested by each cooperator. The plethora of data needed for a breed conclusion was not possible.

Previous research of PAP has been attempted in a multitude of breeds. Table **2.3** lists different breeds of cattle that have been PAP tested in previous research. No one breed of cattle appears to be resistant to high-altitude hypoxia, as high PAP values have been found in all breeds tested (Crawford et al., 2015).

Table 2.3 List of cattle breeds that have been PAP[i] tested and the corresponding citation

Breed	Reference
Angus	Ahola et al. (2006); Shirley et al. (2008); Crawford et al. (2015)
Hereford	Busch et al. (1985); Rhodes (2005); Crawford et al. (2015)
Red Angus	Schimmel (1981); Crawford et al. (2015)
Simmental	Hays and Bianca (1976); Crawford et al. (2015)
Gelbvieh	Han et al. (2008); Crawford et al. (2015)
Holstein	Rudolph and Yuan (1966); Stenmark et al. (1987)
Jersey	Reeves and Leathers (1964); Reeves et al. (1972)
Brown Swiss	Hays and Bianca (1976); Stenmark et al. (1987)
Friesian	Amory et al. (1992)
Belgian White & Blue	Gustin et al. (1988); Amory et al. (1992)
Stabilizer composite	Neary et al. (2013)
Charolais	Crawford et al. (2015)
Limousin	Crawford et al. (2015)
Maine Anjou	Crawford et al. (2015)
Saler	Crawford et al. (2015)

[i] Pulmonary arterial pressure

2.4.4.2 Sex

There are several studies that report differences in PAP between sexes. Female adult rats are less hypertensive than males as reported by Rabinovitch et al. (1981). They speculated that females have fewer muscularized alveolar wall arteries than males. Cockrum et al. (2014) reported a heritability of PAP was different between heifers and bulls, 0.21 ± 0.04 and 0.38 ± 0.08, respectively in a genetic evaluation of PAP in Angus cattle raised at high elevation (2,170 m). The authors also found a genetic correlation of 0.64 ± 0.14 between bulls and heifers. This suggested PAP may be considered a different trait among sexes. Pulmonary hypertension may be influenced by hormonal differences between the sexes, indicated by both studies. Holt and

Callan (2007), however, claimed there is no physiological basis for the differences in PAP measurements, and that differences may be due to differential management practices of the sexes. Cockrum et al. (2019) supported this statement, as bulls are typically managed to gain 1.5 kg/d from weaning to yearling in a gain test, whereas heifers are typically forage raised and gain 0.5 kg/d.

2.4.4.3 Age

Young animals' lungs are not fully mature and more susceptible to the effects of hypoxia (Stenmark et al., 2009). Infant rats under hypoxic conditions showed that as lung volume increased, alveoli in the lungs did not multiply normally. This suggested that vascular remodeling from hypoxia did not permit normal alveolar multiplication. Thus, this decreased total alveolar surface area and decreased oxygen utilization ability (Rabinovitch et al., 1981). Holt and Callan (2007) stated that accuracy of PAP testing is better in cattle at 12 months of age and older. However, as an animal ages, mean PAP measurement increases in the observations. Enns et al. (1992) reported that PAP observations increased be 0.0387 mmHg per day of age in an Angus herd located at an elevation of 2,070 m. This could be due to the natural stiffening of blood vessels as animals age (Lam et al., 2009). It has not been studied at what age this increase in PAP per day plateaus.

2.4.4.5 Illness

Illnesses can cause concurrent high intrapulmonary arterial pressures. Some of these illnesses are: congenital heart disease, mitral stenosis, recurrent pulmonary embolism, primary parenchymal disease of the lung, and idiopathic or primary pulmonary hypertension (Alexander

and Jensen, 1963). Viral, bacterial and parasitic infections may also increase susceptibility to PH. Thus, PAP observations from sick animals should not be considered reliable (Holt and Callan, 2007).

Many respiratory diseases fall under the umbrella of Bovine Respiratory Disease (BRD). Gram negative sepsis also has the ability to elevate PAP scores and increase an animal's susceptibility to PH (Tikoff et al. 1966; Reeves et al., 1972, 1973). Holt and Callan (2007) postulated that treatment of cattle with flunixin meglumine may be clinically helpful in blocking the effect of endotoxin on PH.

2.4.4.6 Environmental/Elevation

Elevation has historically been the biggest environmental influence on PAP. The study by Holt and Callan (2007) stated that hypoxic conditions which stimulate a pulmonary response are not seen until approximately 1,524 m. The degree of pulmonary vasoconstriction and hypertension increases as the individual increases in elevation (Des Jardin, 2002). Holt and Callan (2007) report an increase in 1-2 mmHg for every 305 m increase in elevation above 1,524 m. Pulmonary arterial pressure observations above 1,524 m should only be considered a reliable predictor for susceptibility to PH caused by elevation. Cattle need to be allowed to acclimate at elevation for at least 3 weeks prior to testing (Holt and Callan, 2007). Cold temperatures also may cause an increase in PAP and vascular resistance and can cause a fall in arterial oxygen tension (Will et al. 1978). A 25-55% increase in PAP observations was seen in cattle exposed to 0°C for at least 48 h prior to measurement. After 48 h, with increased oxygen supplemented, PAP measurements returned to original levels. This response suggested that the increase in pressure was likely due to an increase in pulmonary blood flow during the cold exposure.

High growth rates in cattle could be a contributing factor in the increased PAP observations (Jensen et al., 1976; Neary et al., 2015; Viet and Farrell, 1978). Direct effects from selection for growth, such as weaning weight and yearling weight, in Angus cattle have been increasing dramatically for approximately the last 30 years. The average increase in weaning weight was 1.5 kg per year, and the average increase in yearling weight was calculated as 2.8 kg per year. This makes estimating the strength of the genetic relationship between PAP and the aforementioned traits important. However, Crawford et al. (2016) found only slight positive relationships between growth and PAP, such it is possible to improve growth rate of Angus cattle without detrimental effects on PAP. Previous studies of this correlation resulted in significantly different estimates from Shirley et al. (2008). This could be in part that early computational power was not as strong as more recent studies' computing power, and as such earlier estimates may not be as reliable.

The potential antagonist relationship between PAP and production traits such as weight-related feedlot characteristics is important to understand due to the emphasis of selection for PAP. The majority of reported genetic correlations between PAP and yearling weight are low, however it is important to further study the influence of feedlot characteristics and its overall influence on PAP and vice versa. Cattle entering a feedlot system have typically shown an increase in mPAP throughout the finishing phase due to adipose tissue and ruminal engorgement increase (Neary et al, 2015). Increased intake of concentrates and rapid weight gain due to the feedlot environment increased the work of cardiac ventricles (Jensen et al., 1976). Jensen et al. (1976) conducted a study across 4 commercial feedlots at an elevation of 1,600 m and found that 5.6% of cattle suffered from symptoms associated with PH.

There is currently little research that analyzes the genetic relationship between PAP and feedlot efficiency traits. Animals with a lower PAP exhibited lower feed intake which in turn corresponds to a reduced feed efficiency when compared to similar animals with a high PAP (Maddock et al., 2010). In another study, phenotypic correlations between PAP and average daily intake (-0.072) and average daily gain (0.061) suggested that animals selected for ideal mPAP do not experience decreased feedlot performance (Boldt et al., 2014).

Positive relationship trends between PAP, muscle development, and growth have been reported (Pauling et al., 2017). Fat deposition and muscle mass increases may also lead to an increase in PAP as reported by Jensen et al. (1976) and Neary et al. (2015). Hypertensive tendencies could be triggered by the increase vascular adipose tissue and rapid body size growth, which generates cardiac stress. Pauling et al. (2017) reported a moderate positive genetic correlation between PAP and ultrasound ribeye area which may support the above theory.

2.5 Data

2.5.1 Statistical Estimates

Animal breeders developed mixed linear models to evaluate genetic potential in bulls. This allowed models to account for both fixed effects and random effects. These models gained in usage with the advancement in computer software, technology, and processing power.

Studies that contain higher levels of data may be using reaction norm models. reaction norm models are statistical methodologies that allow the description of genetic and phenotypic patterns across environmental gradients (Santana et al., 2015; Mota et al., 2015; Oliveira et al., 2018; Speidel et al., 2020). The usage of these models can allow for more precise descriptions of genetic relationships between different elevations.

Past research has described differing levels of regression to account for the mean relationship between PAP and elevation. Typical fixed effects are sex, age in days, and contemporary groups. Individual animal, contemporary groups, and sires may also be considered for random effects. Higher orders of regression may be considered but may not account for additional variation (Speidel et al., 2020). Model building exercises are described by Crawford et al. (2016b). The general form of a random regression is presented in matrix form below:

$$y = Xb + Qu + Zcg + e,$$

where y represents the vector of observations recorded; X is the incidence matrix relating observations in y to fixed effects in b; Q represents the incidence matrix of covariates relating the observations in y to random genetic regression coefficients in u; Z is a known incidence matrix relating observations in y to random effects in cg; and e is a vector of random residuals. Animal Breeder's Toolkit (Golden et al., 1992) and the statistical software package ASREML 3.0 (Gilmour et al., 2009) are often used in the implementation of ancestral pedigree construction.

Observations of PAP have been noted to have a right-tailed distribution skew (Zeng et al., 2016; Pauling et al., 2018; Cockrum et al., 2019; Speidel et al., 2020). This issue often violates the statistical assumptions of normality and as such it is statistically suggested to transform the data. However, past research in PAP has discovered that raw PAP observations may be utilized instead of Box-Cox transformed data (Zeng, 2016; Pauling et al., 2018; Speidel et al., 2020). Some reasons for not utilizing transformed data are issues with resulting parameter estimates not being representative of observed data scale and back transformation difficulties due to non-linearity. Also, given that individuals that are located on the right-tailed skew are animals whose phenotypes we would like to evaluate in the full extent, it would not make sense to remove the magnitude of their distribution outside the normal assumptions. While animals with these

phenotypes are usually small in number and extreme, they are extremely valuable to the understand of the relationship between PAP and risk of HAD (Speidel et al., 2020).

2.5.2 Repeatability and Repeated Measures

The term "repeated measures" typically refers to multiple responses, or observations, taken in sequence on the same experimental unit, in this case usually an animal. Observations are often taken over time. Repeated measures experiments are a type of factorial experiment, with time and potential treatment or change as factors. Objectives of repeated measures analysis are to examine and compare response or observation trends over time. This can involve comparisons between changes and time or comparison of times within a treatment/change. This is a common component of any factorial experiment. Repeated measures analysis requires special attention is the correlation pattern among observations on the same animal over time (Littell et al., 1998). Repeated measures are crucial from a disease physiology standpoint because they account for within animal variation (Littell et al., 1998).

2.5.3 Quantitative Genetic Evaluations of PAP

Pulmonary vascular responses to hypoxia were suggested to be genetically influenced by Will et al. (1975), although it was unknown at the time of the study the weight of the influence. Disease management, historically, has been focused on modification of environment; not focusing on the potential for genetic improvement of health traits. The incidence of RHF and PH is difficult to determine in a beef cattle herd because the proper diagnosis of disease affected animals in a range environment is challenging. For this reason, PAP measures in cattle are used to indicate susceptibility to PH as an indicator trait. PAP measurements are only accurate at 1,524 m and above, and when animals are acclimated to that elevation for at least 21 days, as

stated by Holt and Callan (2007). Due to this, lower altitude cattle producers typically do not collect PAP observations due to the lack of economic incentive. This low altitude limitation creates a need for the development of indicator traits that are genetically correlated to the trait of interest, as stated by Enns et al. (2011). However, there is research being done to determine if around 1,524 m is a high enough elevation or if it should be considered a moderate elevation and a separate indicator trait measurement. There may be increasing economic incentive for lower altitude PAP measurement due to the increased prevalence of feedlot heart disease (FHD) at lower altitudes.

Colorado State University has been conducting extensive research to evaluate genetic variability of PAP and correlated traits. PAP is moderate to highly heritable (0.20 – 0.77) in Angus and Hereford cattle, as shown by this research. These results suggest that the selection of lower PAP observations in replacement animals can and will lead to lower PAP observation in the selected individual's progeny. Table **2.4** describes PAP heritability estimates obtained from cattle as previously reported.

Table 2.4 Pulmonary arterial pressure heritability estimates (SE) previously reported.

Source	Full[1]	Bull	Heifer	Steer	Breed
LeValley, (1978)	0.42 (0.20)[2] 0.66 (0.21)[3] 0.53 (0.27)[4]	-	-	-	Angus and Hereford
Schimmel, (1981)	0.40 (0.13)	0.60 (0.24)	0.77 (0.21)	-	Angus and Hereford
Enns et al., (1992)	0.46 (0.16)	-	-	-	Angus
Shirley et al., (2008)	0.34 (0.05)	-	-	-	Angus
Cockrum et al., (2014)	0.31 (0.03)	0.38 (0.08)	0.21 (0.04)	0.20 (0.15)	Angus
Zeng et al., (2014)	-	-	0.22 (0.04)	-	Angus
Crawford et al., (2016)	0.26 (0.03)	-	-	-	Angus
Pauling et al., (2018)	0.34 (0.03)	-	-	-	Angus
Speidel et al., (2020)	0.22 – 0.41	-	-	-	Angus

[1] Heritability estimate obtained from both sexes
[2] Estimate for first pulmonary arterial pressure taken
[3] Estimate for second pulmonary arterial pressure taken
[4] Estimate for third pulmonary arterial pressure taken

The initial estimated for heritability of PAP were moderate to high (LeValley, 1978; Schimmel, 1981; Enns et al, 1992), while more recent estimates within the last decade are low to moderate (Cockrum et al, 2014; Crawford et al, 2016; Shirley et al, 2008; Zeng et al, 2014). Heritability estimates from publications by Cockrum, Crawford, and Zeng were obtained using data from Colorado State University Beef Improvement Center, utilizing yearling PAP observations and weanling PAP observations.

Pulmonary Arterial Pressure EPDs for Colorado State University Beef Improvement Center (Saratoga, WY; 2,170 m) and the Tybar Ranch (Carbondale, CO; 1,880 m) were calculated by Enns et al. (2011). The EPDs were then used as selection criteria for both herds. This implementation of PAP EPD data yielded a downward trend in average PAP EPD values in both herds. Research has shown selection for lower PAP observations may be successful, however, death loss due to PH in these calf crops has not been reported. These data sets are challenging due to the use of outside sires through artificial insemination (AI). Many of the AI sires are not raised in high altitude and will likely not have PAP observations. This makes progeny performance hard to predict at high elevations.

Early studies of the correlation between PAP and weight traits resulted in significantly different estimates from Shirley et al. (2008) and Crawford et al. (2016) studies. This could be in part that early computational power was not as strong as more recent studies' computing power, and as such earlier estimates may not be as reliable. The more recent studies listed both estimated a moderate genetic correlation between PAP and direct weaning weight in Angus cattle. Both studies also reported a positive genetic relationship between PAP and direct birth weight, however there was a magnitude difference, likely due to differences in sample populations.

2.5.4 Multivariate Models

Multivariate models use information from multiple traits and the genetic and residual relationships between the traits, instead of just utilizing information from one trait like the univariate model. Selection of livestock evaluates many different traits for performance and economic importance. Many traits considered of importance are genetically and (or) phenotypically related. The use of multiple traits in an evaluation is considered ideal because it can account for relationships between traits (Mrode et al., 2014). Prediction error variance (PEV) decreases in multivariate model usage and corresponds with an increase in accuracy (Schaeffer et al., 1984). Lowly heritable traits benefit the most from the use of multivariate analysis. The increased accuracy for lowly heritable traits is due to an increase of information stemming from residual covariance between traits (Thompson and Meyer, 1986; Mrode et al., 2014).

Multivariate analysis can help operations avoid introducing culling bias into their selection decisions (Mrode et al., 2014). Prediction of breeding values for non-recorded or lowly observed traits that are correlated is possible using multivariate analysis (Schaeffer et al., 1984). The removal of culling bias is possible because the analysis includes the last reported trait as a genetically related trait (Mrode et al., 2014).

Below is the multivariate model shown in matrix notation (Mrode, 2014).

$$\begin{bmatrix} \boldsymbol{y_1} \\ \boldsymbol{y_2} \end{bmatrix} = \begin{bmatrix} \boldsymbol{X_1} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{X_2} \end{bmatrix} \begin{bmatrix} \boldsymbol{\beta_1} \\ \boldsymbol{\beta_2} \end{bmatrix} + \begin{bmatrix} \boldsymbol{Z_1} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{Z_2} \end{bmatrix} \begin{bmatrix} \boldsymbol{u_1} \\ \boldsymbol{u_2} \end{bmatrix} + \begin{bmatrix} \boldsymbol{e_1} \\ \boldsymbol{e_2} \end{bmatrix},$$

where $\mathbf{y_i}$ was a vector of observations for the traits corresponding to the *ith* trait, $\mathbf{X_i}$ and $\mathbf{Z_i}$ were known incidence matrices relating observations in $\mathbf{y}$ to levels of fixed effects in $\boldsymbol{\beta}$, and random solutions in $\mathbf{u}$, respectively, and $\mathbf{e_i}$ was a vector of random residuals. Variances and means for random effects included in the model are as follows:

$$Var\begin{bmatrix}u_1\\u_2\end{bmatrix} = \begin{bmatrix}\sigma_1^2 & \sigma_{12}\\\sigma_{21} & \sigma_2^2\end{bmatrix} \otimes A \text{ and } Var\begin{bmatrix}e_1\\e_2\end{bmatrix} = \begin{bmatrix}\sigma_{e_1}^2 & \sigma_{e_{12}}\\\sigma_{e_{21}} & \sigma_{e_2}^2\end{bmatrix} \otimes I \text{ and } E\begin{vmatrix}\mu\\e\end{vmatrix} = \begin{vmatrix}0\\0\end{vmatrix}$$

Where **A** was Wright's numerator relationship matrix, and **I** was an identity matrix of whose order was equal to the number of animals with each respective phenotype (Wright, 1922).

There are disadvantages to using a multivariate analysis approach. Multivariate analysis requires more computational power (memory and disk storage) and time when compared with a univariate analysis. There is also a shortcoming regarding smaller data sets, as the key to successful multivariate analysis is accurate estimation of genetic and residual correlations which is problematic in small data sets.

2.5.5 Genetic Correlations

Bourdon (1997) defined genetic correlation as the relationship between breeding values of one trait and the breeding values of another trait. Selection for one trait can influence the expression of another trait when they are genetically correlated. In addition to this, performance in one trait can be used in the prediction of the performance in a genetically correlated trait.

It is crucial to understand that relationship between PAP at moderate elevation and PAP at high elevation for example. Another example is the correlation between age and PAP. This is important to understand due to calculation of EPD for PAP and producers at moderate and high elevations. Knowing the correlation between high elevation PAP and moderate elevation PAP will help increase the information knowledge used in construction of accurate EPD. This is also helpful for high altitude producers purchasing cattle at lower altitudes and how those cattle will perform at high altitude.

LITERATURE CITED

Ahola, J. K., R. M. Enns, and T. N. Holt. 2006. Examination of potential methods to predict pulmonary arterial pressure score in yearling beef cattle. J. Anim. Sci. 84:1259-1264.

Ahola, J. K., R. M. Enns, and T. Holt. 2006. Examination of potential methods to predict pulmonary arterial pressure score in yearling beef cattle. J. Anim. Sci. 84:1259-1264.

Alexander, A., D. Will, R. Grover, and J. Reeves. 1960. Pulmonary hypertension and right ventricular hypertrophy in cattle at high altitude. Am. J. Vet. Res. 21:199-204.

American Angus Association. 2019. Research PAP EPD launched by Angus Genetics Inc. Available from https://www.angus.org/Pub/Newsroom/Releases/020119-pap-epd-launch.aspx [accessed June 12, 2021].

Angel, K. L., and J. W. Tyler. 1992. Pulmonary Hypertension and Cardiac lnsufficiency in Three Cows with Primary Lung Disease. J. Vet. Intern. Med. 6:214-219.

Beede, D., and R. Collier. 1986. Potential nutritional strategies for intensively managed cattle during thermal stress. J. Anim. Sci. 62:543-554.

Bourdon, R.M. 1997. Understanding Animal Breeding. Prentice-Hall. p 185-239.

Bourdon, R. 1999. Understanding Animal Breeding 2nd. Prentice Hall, Upper Saddle River, New Jersey. p. 161-250.

Boldt, R. J., M. M. Culbertson, N. F. Berge, M. G. Thomas, T. N. Holt, S. E. Speidel, and R. M. Enns. 2014. Phenotypic Analysis of Pulmonary Arterial Pressure and Feed Intake Data in Angus Cattle. Proceedings of the World Congress on Genetics Applied to Livestock Production. Genetic Improvement Programs: Selection for harsh environments and management of animal genetic resources:031.

Busch, M. A., A. Tucker, and D. Robertshaw. 1985. Interaction between cold and altitude exposure on pulmonary circulation of cattle. J. Appl. Physiol. 58:948-953.

Cockrum, R. R., X. Zeng, N. F. Berge, J. M. Neary, F.B. Garry, T. N. Holt, H. D. Blackburn, S. Thomas, S. E. Speidel., D. J. Garrick, R. M. Enns, and M. G. Thomas. 2014. Angus cattle at high altitude: genetic relationships and initial genome wide association analyses of pulmonary arterial pressure. In Proc. 10th World Cong. Genet. Appl. Livest. Prod., Vancouver, British Columbia, Canada.

Cockrum, R. R., S. E. Speidel, N. F. Crawford, X. Zeng, H. D. Blackburn, T. Holt, R. M. Enns, and M. G. Thomas. 2019. Genotypes identified by genome wide association analyses influence yearling pulmonary arterial pressure and growth traits in Angus heifers from a

high-altitude beef production system. *Livest. Sci*. **224**:75–86. doi:10.1016/j.livsci.2019.04.004

Crawford, N. F. 2015. Pulmonary arterial pressure as an indicator for high altitude disease in cattle: breed differences and relationships with growth performance. M.S. Thesis. Colorado State University, Fort Collins, Colorado.

Crawford, N. F., X. Zeng, S. J. Coleman, T. N. Holt, S. E. Speidel, R. M. Enns, J. H. Newman, R. Hamid, and M. G. Thomas. 2016a. 0169 Pulmonary arterial pressure in yearling Angus cattle managed at high altitude: Study of a non-synonymous SNP in the oxygen dependent degradation domain of the endothelial PAS domain-containing protein 1 gene. J. Anim. Sci. 94(Suppl5):82-82. doi:10.2527/jam2016-0169

Crawford N. F., M. G. Thomas, T. N. Holt, S.E. Speidel, and R. M. Enns. 2016b. Heritabilities and genetic correlations of pulmonary arterial pressure and performance traits in Angus cattle at high altitude. J. Anim. Sci. 94:4483-4490.

Des Jardin, T. R. 2002. Cardiopulmonary anatomy and physiology: essentials for respiratory care. Delmar/Thomson Learning, Australia.

Elzinga, G., and N. Westerhof. 1973. Pressure and flow generated by the left ventricle against different impedances. Circ. Res. 32:178-186.

Enns, R. M., J. Brinks, R. Bourdon, and T. Field. 1992. Heritability of pulmonary arterial pressure in Angus cattle. In Proc. West. Sect. Am. Soc. Anim. Sci. 43:111-112.

Enns, R. M., B. W. Brigham, C. M. McAllister, and S. E. Speidel. 2011. Evidence of genetic variability in cattle health traits: opportunities for improvement. Role of genetic evaluation technology in enhancing global competitiveness. Proceedings, Beef Improvement Federation Conference.

Farber, H. W., and J. Loscalzo. 2004. Pulmonary arterial hypertension. New Eng. J. Med. 351:1655-1665.

Fessler, H. E. 2005. Collateral ventilation, the bane of bronchoscopic volume reduction. Am. J. Respir. Crit. Care Med. 171:423-424.

Fregly, M. J. 2011. Adaptations: some general characteristics. Compr. Physiol. p. 3-15. doi: 10.1002/cphy.cp040101

Gilmour, A. R., B. J. Gogel, B. R. Cullis, and R. Thompson. 2009. *ASReml User Guide Release 3.0.* Hemel Hempstead (UK): VSN International Ltd. www.vsni.co.uk [accessed June 12, 2021].

Glover, G. H., and I. E. Newsom. 1917. Brisket Disease: Bulletin. No. 204. Colorado Agricultural College, Fort Collins, Colorado.

Golden, B. L., W. M. Snelling, and C. H. Mallinckrodt. Animal Breeder's ToolKit: user's guide and reference manual. Fort Collins (CO): Colorado State University Agricultural Experiment Station; 1992. Technical Bulletin No.: LTB92-2.

Heath, D., D. Williams, and J. Dickinson. 1984. The pulmonary arteries of the yak. Card. Res. 18:133-139.

Hecht, H. H. 1956. Heart failure and lung disease. Circulation. 14:265-290.

Hohenboken, W., T. Jenkins, J. Pollak, D. Bullock, and S. Radakovich. 2005. Genetic improvement of beef cattle adaptation in America. In: Proc. 37th Beef Improvement Federation Research Symposium and Annual Meeting. p. 115-120.

Holt, T. N., and R. J. Callan. 2007. Pulmonary arterial pressure testing for high mountain disease in cattle. Vet. Clin. N. Am: Food Anim. Pract. 23:575-596.

Humbert, M., N. W. Morrell, S. L. Archer, K. R. Stenmark, M. R. MacLean, I. M. Lang, B. W. Christman, E. K. Weir, O. Eickelberg, and N. F. Voelkel. 2004. Cellular and molecular pathobiology of pulmonary arterial hypertension. J. Am. Coll. Cardiol. 43:S13-S24.

Jaenke, R. S., and A. F. Alexander. 1973. Fine structural alterations of bovine peripheral pulmonary arteries in hypoxia-induced hypertension. Am. J. Pathol. 73:377.

James, L., K. Panter, H. Broquist, and W. Hartley. 1991. Swainsonine-induced high mountain disease in calves. Vet. Hum. Toxicol. 33:217-219.

Jensen, R., R. E. Pierson, P. M. Brady, D. A. Saari, A. Benitez, D. P. Horton, L. H. Lauerman A. E. McChesney, A. F. Alexander, and D. H. Will. 1976. Brisket disease in yearling feedlot cattle. J. Am. Vet. Med. Ass. 169:515-517.

Johnson, H. D., and W. J. Vanjonack. 1976. Effects of environmental and other stressors on blood hormone patterns in lactating animals. J. Dairy Sci. 59:1603-1617.

Kessler, Beth A. *Hedonic Analysis of Yearling Bull Prices for a Land Grant University: Determining the Value of a Pulmonary Arterial Pressure (PAP) Score*, Colorado State University, Ann Arbor, 2013. *ProQuest*, https://ezproxy2.library.colostate.edu/login?url=https://www.proquest.com/dissertations-theses/hedonic-analysis-yearling-bull-prices-land-grant/docview/1496772980/se-2?accountid=10223.

Kuida, H., H. H. Hecht, R. L. Lange, A. M. Brown, T. J. Tsagaris, and J. L. Thorne. 1963. Brisket Disease. III. Spontaneous Remission of Pulmonary Hypertension and Recovery from Heart Failure. J. Clin. Invest. 42:589-596.

Kuriyama, T., and W. W. Wagner. 1981. Collateral ventilation may protect against high-altitude pulmonary hypertension. J. Appl. Physiol. 51:1251-1256.

Lacetera, N., U. Bernabucci, D. Scalia, L. Basiricò, P. Morera, and A. Nardone. 2006. Heat stress elicits different responses in peripheral blood mononuclear cells from Brown Swiss and Holstein cows. J. Dairy Sci. 89:4606-4612.

Lam, C. S., B. A. Borlaug, G. C. Kane, F. T. Enders, R. J. Rodeheffer, and M. M. Redfield. 2009. Age-associated increases in pulmonary artery systolic pressure in the general population. Circ. 119:2663-2670.

LeValley, S. B. 1978. Pulmonary hypertension in beef cattle: a herd study. M.S. Thesis, Colorado State University, Fort Collins, Colorado.

Littell, R. C. (University of Florida, et al. "Statistical Analysis of Repeated Measures Data Using SAS Procedures." *Journal of Animal Science*, vol. 76, no. 4, Am Soc Animal Sci, 1998, pp. 1216–31, doi:10.2527/1998.7641216x.

Maddock, T. D., G. H. L. Marquexini, V. R. G. Mercadante, and G. C. Lamb. 2010. physiology and management. Journal of Dairy Science. 93:683.

Malherbe, C. R., J. Marquard, D. E. Legg, K. M. Cammack, and D. O'Toole. 2012. Right ventricular hypertrophy with heart failure in Holstein heifers at elevation of 1,600 m. J. Vet. Diag. Invest. 24:867-877.

Mota, R. R., R. J. Tempelman, P. S. Lopes, I. Aguilar, F. F. Silva, and F. F. Cardoso. 2016. Genotype by environment interaction for tick resistance of Hereford and Braford beef cattle using reaction norm models. *Genet. Sel. Evol*. **48**:3. doi:10.1186/ s12711-015-0178-5

Mrode, R. A. 2014. Linear Models for the Prediction of Animal Breeding Values: 3rd Edition. CABI.

Nardone, A., B. Ronchi, N. Lacetera, M. S. Ranieri, and U. Bernabucci. 2010. Effects of climate changes on animal production and sustainability of livestock systems. Livest. Sci. 130:57-69.

Neary, J. M., C. W. Booker, B. K. Wildman, and P. S. Morley. 2016. Right-sided congestive heart failure in north American feedlot cattle. J. Vet. Intern. Med. 30:326-334.

Neary, J. M., F. B. Garry, T. N. Holt, M. G. Thomas, and R. M. Enns. 2015. Mean pulmonary arterial pressures in Angus steers increase from cow-calf to feedlot-finishing phases. J. Anim. Sci. 93:3854-3861.

Neary, J. M., D. H. Gould, F. B. Garry, A. P. Knight, D. A. Dargatz, and T. N. Holt. 2013a. An investigation into beef calf mortality on five high altitude ranches that selected sires with low pulmonary arterial pressures for over 20 years. J. Vet. Diag. Invest. 25:210-218.

Neary, J. M. 2013b. Pre-weaned beef calf morality on high altitude ranches in Colorado. M.S. Thesis. Colorado State University, Fort Collins, Colorado.

Neary, J. M. 2014. Epidemiological physiological and genetic risk factors associated with congestive heart failure and mean pulmonary arterial pressure in cattle. Ph. D. Dissertation. Colorado State University, Fort Collins, Colorado.

Neary, M. T., J. M. Neary, G. K. Lund, T. N. Holt, F. B. Garry, T. J. Mohun, and R. A. Breckenridge. 2014. Myosin heavy chain 15 is associated with bovine pulmonary arterial pressure. Pulm. Circ. 4:496-503.

Newman, J. H. T. N. Holt, L. K. Hedges, B. Womack, S. S. Memon, E. D. Willers, L. Wheeler, J. A. Philips, and R. Hamid. 2011. High-altitude pulmonary hypertension in cattle (brisket disease): candidate genes and gene expression profiling of peripheral blood mononuclearcells. Pulm. Circ. 1: 462-469.

Newman, J. H., T. N. Holt, J. D. Cogan, B. Womack, J. A. Philips, C. Li, Z. Kendall, K. R. Stenmark, M. G. Thomas, R. D. Brown, S. R. Riddle, J. D. West, and R. Hamid. 2015. Increased prevalence of EPAS1 variant in cattle with high-altitude pulmonary hypertension. Nat. Comm. 6:6863.

Oliveira, D. P., D. A. L. Lourenco, S. Tsuruta, I. Misztal, D. J. A. Santos, F. R. de Araújo Neto, R. R. Aspilcueta-Borquis, F. Baldi, R. Carvalheiro, G. M. F. de Camargo, *et al.* 2018. Reaction norm for yearling weight in beef cattle using single-step genomic evaluation. *J. Anim. Sci*. **96**:27–34. doi:10.1093/jas/skx006

Panter, K. E., L. F. James, D. Nielson, R. J. Molyneux, M. H. Ralphs, and J. D. Olsen. 1988. The relationship of *Oxytropis sericea* (green and dry) and *Astragalus lentiginosus* with high mountain disease in cattle. Vet. Hum. Toxicol. 30:318.

Pauling, R. C., S. E. Speidel, M. G. Thomas, T. N. Holt, and R. M. Enns. 2018. Evaluation of moderate to high elevation effects on pulmonary arterial pressure measures in Angus cattle1. *J. Anim. Sci*. **96**:3599–3605. doi:10.1093/jas/sky262

Peek, S. F., and S. M. McGuirk. 2008. Cor pulmonale. In: T. J. Divers and S. F. Peek (eds.) Rebhun's Diseases of Dairy Cattle 2nd. Saunders Elsevier, St. Louis, MO. p. 58-59.

Pendlum, L., J. Boling, L. Bush, and R. Buckner. 1980. Digestibility and metabolism of Kenhy tall fescue harvested at three stages of physiological maturity. J. Anim. Sci. 51:704-711.

Pierson, R. E., and R. Jensen. 1956. Brisket disease. In: M. G. Fincher, W. J. Gibbons, K. Mayer and S. E. Park (eds.) Diseases of cattle. American Veterinary Publications, Evanston, IL. p. 717-723.

Rabinovitch, M., W. J. Gamble, O. S. Miettinen, and L. Reid. 1981. Age and sex influence on pulmonary hypertension of chronic hypoxia and on recovery. Am. J. Phys. Heart. Circ. Phys. 240:H62-H72.

Reeves, J. T., F. S. Daoud, and M. Estridge. 1972. Pulmonary hypertension caused by minute amounts of endotoxin in calves. J. Appl. Physiol. 33:739-743.

Reeves, J. T., F. S. Daoud, and M. Estridge. 1973. Endotoxin: a cause of spontaneous pulmonary hypertension in cattle? Am. J. Vet. Res. 34:1573-1576.

Reeves, J. T., and J. E. Leathers. 1967. Postnatal development of pulmonary and bronchial arterial circulations in the calf and the effects of chronic hypoxia. Anat. Rec. 157:641- 655.

Rhodes, J. 2005. Comparative physiology of hypoxic pulmonary hypertension: historical clues from brisket disease. J. Appl. Physiol. 98:1092-1100.

Salman, M., M. King, K. Odde, and R. Mortimer. 1991a. Costs of veterinary services and vaccines/drugs used for prevention and treatment of diseases in 86 Colorado cow-calf operations participating in the National Animal Health Monitoring System (1986-1988). J. Am. Vet. Med. Assoc. 198:1739-1744.

Salman, M. D., M. E. King, K. G. Odde, and R. G. Mortimer. 1991b. Annual costs associated with disease incidence and prevention in Colorado cow-calf herds participating in rounds 2 and 3 of the National Animal Health Monitoring System from 1986 to 1988. J. Am. Vet. Med. Assoc. 198:968-973.

Santana, M. L. Jr, J. P. Eler, A. B. Bignardi, A. Menéndez-Buxadera, F. F. Cardoso, and J. B. Ferraz. 2015. Multi-trait linear reaction norm model to describe the pattern of phenotypic expression of some economic traits in beef cattle across a range of environments. *J. Appl. Genet*. **56**:219–229. doi:10.1007/ s13353-014-0242-9

Schaeffer, L. 1984. Sire and cow evaluation under multiple trait models. J. Dairy Sci. 67:1567-1580.

Schimmel, J. G., and J. Brinks. 1982. The relationship of pulmonary arterial pressure with postweaning performance traits in yearling beef bulls. In: Proc. West. Sect. Amer. Soc. Anim. Sci. p 203-205.

Schimmel, J. G. 1981. Genetic aspects of high mountain disease in beef cattle. Ph.D. Dissertation. Colorado State University, Fort Collins, Colorado.

Shirley, K. L., D. W. Beckman, and D. J. Garrick. 2008. Inheritance of pulmonary arterial pressure in Angus cattle and its correlation with growth. J. Anim. Sci. 86:815-819.

Speidel, S.E., M.G. Thomas, T.N. Holt, R.M. Enns, Evaluation of the sensitivity of pulmonary arterial pressure to elevation using a reaction norm model in Angus Cattle, J. Anim. Sci. Volume 98, Issue 5, May 2020, skaa129, https://doi.org/10.1093/jas/skaa129

Stenmark, K. R., K. A. Fagan, and M. G. Frid. 2006. Hypoxia-induced pulmonary vascular remodeling: cellular and molecular mechanisms. Circ. Res. 99:675-691.

Stenmark, K. R., J. Fasules, D. M. Hyde, N. F. Voelkel, J. Henson, A. Tucker, H. Wilson, and J. T. Reeves. 1987. Severe pulmonary hypertension and arterial adventitial changes in newborn calves at 4,300 m. J. Appl. Physiol. 62:821-830.

Stenmark, K. R., B. Meyrick, N. Galie, W. J. Mooi, and I. F. McMurtry. 2009. Animal models of pulmonary arterial hypertension: the hope for etiological discovery and pharmacological cure. Am. J. Phyis. Lung Cell Mol. Phys. 297: L1013-L1032.

Stuedemann, J. A., and C. S. Hoveland. 1988. Fescue Endophyte: History and Impact on Animal Agriculture. J. Prod. Agric. 1:39-44.

Thomas M.G., J.M. Neary, G.M. Krafsur, T.N. Holt, R.M. Enns, S.E. Speidel, F.B. Garry, A. Canovas, J.F. Medrano, R.D. Brown, and K.R. Stenmark. 2018. Pulmonary hypertension in beef cattle: a complicated threat to health and productivity in multiple beef industry segments. White Paper for Certified Angus Beef. http://www.cabpartners.com/news/research.php. Accepted 5/9/2018.

Thompson, R., and K. Meyer. 1986. A review of theoretical aspects in the estimation of breeding values for multi-trait selection. Livest. Prod. Sci. 15:299-313.

Tikoff, G., H. Kuida, and M. Chiga. 1966. Hemodynamic effects of endotoxin in calves. Am. J. Physiol. 210:847-853.

Tucker, A., I. McMurtry, J. Reeves, A. Alexander, D. Will, and R. Grover. 1975. Lung vascular smooth muscle as a determinant of pulmonary hypertension at high altitude. Am. J. Physiol. 228:762-767.

Tucker, A., and F. Rhodes. 2001. Role of vascular smooth muscle in the development of high altitude pulmonary hypertension: An interspecies evaluation. High Alt. Med. Biol. 2:173-189.

Veit, H. P., and R. L. Farrell. 1978. The anatomy and physiology of the bovine respiratory system relating to pulmonary disease. Cornell Vet. 68:555-581.

Will, D. H., A. F. Alexander, J. T. Reeves, and R. F. Grover. 1962. High altitude-induced pulmonary hypertension in normal cattle. Circ. Res. 10:172-177.

Will, D. H., J. L. Hicks, C. Card, and A. Alexander. 1975a. Inherited susceptibility of cattle to high-altitude pulmonary hypertension. J. Appl. Physiol. 38:491-494.

Will, D. H., J. L. Hicks, C. S. Card, J. T. Reeves, and A. F. Alexander. 1975b. Correlation of acute with chronic hypoxic pulmonary hypertension in cattle. J. Appl. Physiol. 38:495-498.

Will, D. H., J. F. Horrell, J. T. Reeves, and A. F. Alexander. 1975c. Influence of altitude and age on pulmonary arterial pressure in cattle. Proc. Soc. Exp. Biol. Med. 150:564-567.

Will, D. H., I. F. McMurtry, J. T. Reeves, and R. F. Grover. 1978. Cold-induced pulmonary hypertension in cattle. J. App. Phys. 45:469-473.

Williams, J., J. Bertrand, I. Misztal, and M. Łukaszewicz. 2012. Genotype by environment interaction for growth due to altitude in United States Angus cattle. J. Anim. Sci. 90:2152-2158.

Zeng, X., R. R. Cockrum. N. F. Berge. J. M. Neary, F. B. Garry, T. N. Holt. H. D. Blackburn, S. E. Speidel, D. J. Garrick, R. M. Enns, and M. G. Thomas. 2014. Genetic correlation and genome wide association study of pulmonary arterial pressure and post weaning growth traits in Angus heifers from a high altitude breeding program. In Proc. 10th World Cong. Genet. Appl. Livest. Prod., Vancouver, British Columbia, Canada.

Zeng, X. 2016. Angus cattle at high altitude: pulmonary arterial pressure, estimated breeding value and genome-wide association study [Ph.D. dissertation]. Fort Collins (CO): Colorado State University.

Zuckerman, B. D., E. Orton, L. Latham, C. C. Barbiere, K. Stenmark, and J. Reeves. 1992. Pulmonary vascular impedance and wave reflections in the hypoxic calf. J. Appl. Physiol. 72:2118-2127.

CHAPTER III

REPEATED MEASURES OF PAP AT DIFFERENT ELEVATIONS IN BEEF BULLS IN COLORADO

Summary

High Altitude Disease (HAD) in cattle, historically, is a consequence of pulmonary hypertension (PH) induced by hypoxia at elevations > 1,500 m. Pulmonary arterial pressure (PAP) is an indicator of animal susceptibility to HAD and is moderately heritable (h^2 = 0.26 to 0.34). The objective of this study was to analyze repeated measures of PAP in growing beef bulls and estimate correlations across elevations and ages. Data consisted of breed, mPAP measures, elevation, weights, and age from 2018 spring-born bulls at the Colorado State University (CSU) Agriculture Research, Development, and Education Center (ARDEC) with data collected during the years 2018 and 2019. Five PAP measurements were collected from each bull: 1) Weaning PAP at ARDEC (1,525 m); 2) Yearling PAP at ARDEC; 3) PAP after acclimating for 28 days at Fort Lewis College (FLC; 2,470 m), Hesperus, CO; 4) before returning to ARDEC from FLC after 110 days at FLC; and 5) after re-acclimating for 57 days to the moderate elevation at ARDEC when the bulls were 557 ± 2.92 d (18 mo) of age. Due to these procedures, elevation, age and PAP (collection date) were confounded. PAP measurements (mmHg) across these 5 times in Angus (n = 18) and Hereford (n = 12) bulls were: 1) 37.97 ± 0.37; 2) 40.93 ± 0.77; 3) 46.10 ± 1.48; 4) 45.00 ± 1.11; and 5) 42.23 ± 0.67. In the model building exercise for stepwise linear regression analysis, breed and elevation-age were important ($P < 0.05$). Also, PAP changed ($P < 0.05$) across the 5 time periods (i.e., increased with altitude and then declined as bulls returned to moderate altitude).

Furthermore, yearling PAP measurements collected at 1,525 m were highly correlated with PAP measures at 2,470 m PAP, as well as a PAP collected at 18.3 ±0.1 mo of age at 1,525 m (r = 0.93-0.99), respectively. In the Western US, ~10,000 yearling bulls and heifers are PAP tested annually. Most of these cattle are replacements for high elevation beef production systems. Results of this study suggested that the yearling PAP measurement collected at 1,525 m was an adequate predictor of PAP measurement as bulls grew to 18.3 months of age (i.e., both 1,525 and 2,470 m); however, additional PAP testing of cattle at these elevations is warranted as data in this thesis is minimal.

Introduction

Pulmonary arterial pressure (PAP) is an indicator of pulmonary hypertension (PH) and used to determine an individual's susceptibility to High Altitude Disease (HAD). Right-sided heart failure that results from the hypoxic conditions at altitudes greater than 1,500 m is a common pathophysiological observation of HAD (Thomas et al., 2018). Past research indicates that PAP measurements are moderately heritable, which is important when selecting bulls for high altitude beef production systems (Shirley et al., 2008; Crawford et al.,2016; Pauling et al., 2018; Speidel et al., 2020). Bull and heifer development procedures for these systems typically PAP test cattle at approximately one year of age (culling of animals with measurements > 50 mmHg; BIF, 2020). Yearling PAP EPD are now being published; therefore, there is need to learn more about this trait and the many sources of variation (breed, age, altitude, etc.) that may influence breeding value estimations.

This study's over-arching goals were to determine if a bull's lifetime PAP can be determined by a yearling measurement at moderate elevation. We are also determining the impact of changing altitude on a bull's PAP measurements and the relationship between PAP at moderate

altitude (1,525 m) to PAP at high altitude (2,470 m). With expected progeny differences (EPD) for PAP measurement becoming available within breed associations such as American Angus Association (Angus Genetics Inc. 2019), it is important to determine the implications of low to moderate elevation PAP measurements on overall usefulness in estimating high altitude PAP EPD and for the movement of bulls to/from moderate and high elevations. PAP EPD can be utilized to assist in selection decisions by breeding against genetic susceptibility to HAD. However, measurements of PAP determine an animal's own susceptibility to HAD and phenotypic performance at altitude of residence. An animal may be considered to have favorable PAP EPD but have a detrimental phenotypic PAP (mm Hg) measurement. As such, it is important to utilize both phenotypic measurements and EPD when making selection decisions for high altitude production. Due to the aforementioned, the objective of this study was to analyze repeated measures of PAP in growing beef bulls and determine correlations across time-elevation.

Materials and Methods

This study obtained approval from the Colorado State University Animal Care and Use Committee under protocol number 16-6757AA.

Cattle and Data

Pulmonary arterial pressure was measured on Angus and Hereford bulls (n = 18 and n = 12 respectively) at different ages and elevations as the bulls progressed from weaning to yearling to 18 months of age. Cattle were born at an elevation of approximately 1,525 m located at Colorado State University's Agricultural Research, Development, and Education Center (ARDEC) facility located in Fort Collins, CO. Bulls used in this study were calved during 2018 between the months ranging from March and May. Post-weaning, bulls were fed a typical gain test ration (1.5 kg/d)

between weaning (~6 months of age) and yearling (~12 months of age). Subsequently, bulls were moved and grazed irrigated pasture, gaining ~0.5 kg/d at Fort Lewis College (Hesperus, CO) at an elevation of approximately 2,470 m from June to September 2019. The bulls then returned to ARDEC on September 11, 2019. Five PAP measurements were collected from each bull over this time period: 1. Weaning PAP at ARDEC (10/31/2018), 2. Yearling PAP at ARDEC (5/3/2019), 3. After acclimating to high altitude (FLC) (6/27/2019), 4. Before returning to ARDEC from FLC (9/11/2019), and 5. After acclimating again to the moderate altitude at ARDEC (11/13/2019). Due to these data collection procedures, elevation and PAP (collection date) were confounded. It is also important to note that these bulls are from herds in Colorado that are selecting for altitude tolerance. Appendix II (Appendix II: Bull Data) illustrates general characteristics and weight data on these animals.

Statistical Analysis

Model selection was completed using stepwise regression in R to determine the most important terms to be included in the model. The model utilized was a multiple regression model as follows:

$$\boldsymbol{y_i = X_i b + Z_i u + e_i}$$

where $\mathbf{y_i}$ was a vector of PAP observations referring to the trait *i*. $\boldsymbol{X_i}$ was an incidence matrix relating the fixed effects (breed and a confounded variable of elevation and age[time]) in vector $\boldsymbol{b_i}$ to the observations $\mathbf{y_i}$. In addition, the effects of a quadratic random regression of PAP on time within an individual were included as incidence matrix $\boldsymbol{Z_i}$, relating the values of the PAP regression to the observations in $\boldsymbol{y_i}$**.** The value $\boldsymbol{e_i}$ corresponded to the residual errors associated with the vector of PAP observations.

Pulmonary arterial pressure observations used in this study had a skewed right distribution which parallels reports using similar data (Pauling et al., 2018, Cockrum et al., 2019, Speidel et al. 2020). Figures **3.1** and **3.2** illustrate the right-skewed distribution of data, especially as altitude and time increases. These figures show the increasing right-skewed distribution in both Angus and Hereford bulls between yearling PAP measurements and high-altitude PAP measurements. A plot of residuals vs fitted values and a normal quantile-quantile plot were created. These plots suggested that raw phenotypes violate assumptions of normality. As a result of the violation, Tukey transformation analysis suggested that the raw PAP observations be transformed for accommodation of non-normality of data. Resulting parameter estimates after transformation were not representative of original observed data scale, and the back transformation was not logical due to nonlinearity between transformed parameter estimates and original data. Due to these issues, models will be presented from an evaluation of raw PAP phenotypes.

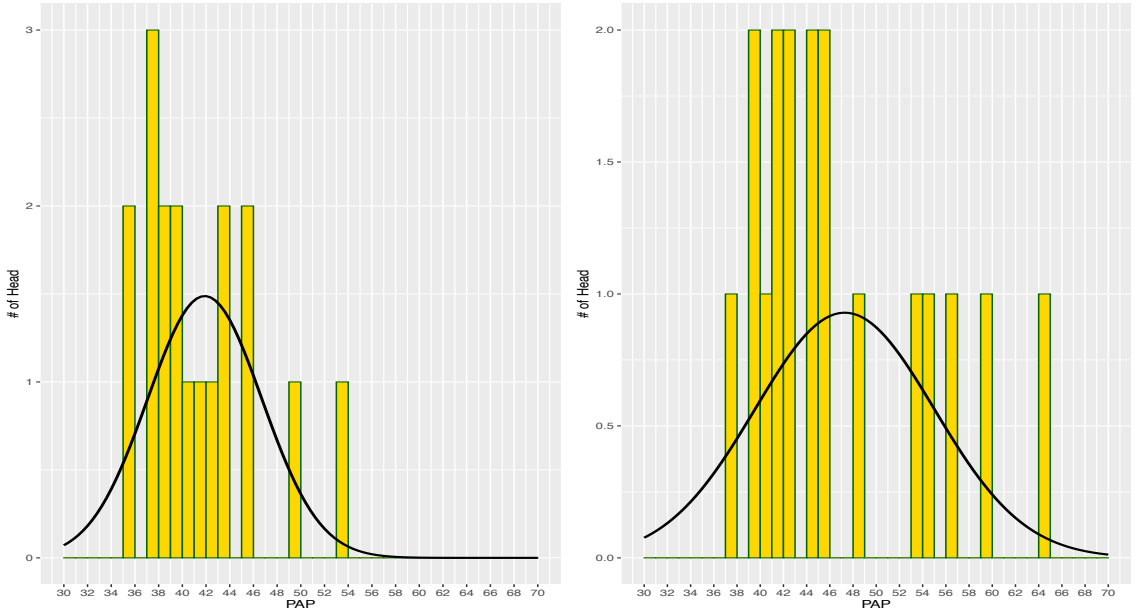

Figure 3.1. Variation among Angus bulls between time 2 (yearling PAP at elevation = 1,525 m) and time 3 (age = 14.0 ± 0.1 mo; elevation = 2,470 m)

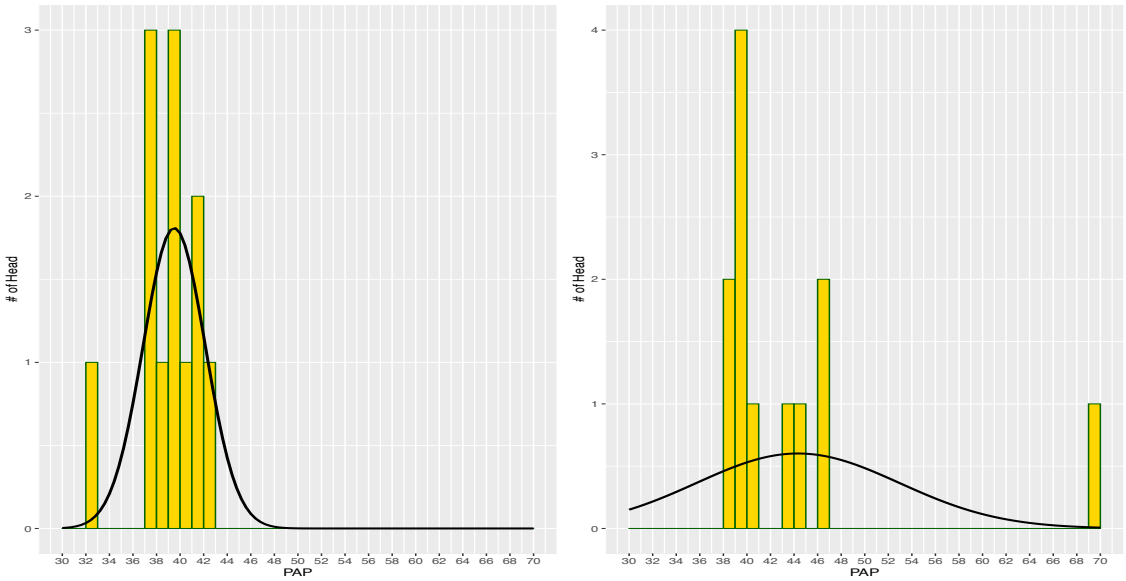

Figure 3.2. Variation among Hereford bulls between time 2 (yearling PAP at elevation = 1,525 m) and time 3 ((age = 14.0 ± 0.1 mo; elevation = 2,470 m)

The data were then analyzed using the statistical software package ASReml 3.0 (Gilmour et al., 2009) to test differences in PAP within individuals at different age-elevation. This was used to determine predicted PAP values. Spearman rank correlations and Pearson correlations for PAP on time (elevation/age confounding) were then evaluated from the fitted values for the regression line.

Results and Discussion

Number of observations, arithmetic PAP means, PAP standard deviation (SD), elevation, ages, body weight, as well as minimum and maximum values for PAP in both Black Angus bulls and Hereford bulls are presented in **Table 3.1** and **3.2**, respectively. Weight data was not gathered at timepoint 3 due to inaccessibility to scale at high elevation. Note the dynamics and increase ($p < 0.05$) in PAP mean and SE as bulls aged and were exposed to higher elevation and then moved back to moderate elevation. This increase ($p < 0.05$) in PAP variability can be observed in **Figures 3.1** and **3.2**. These two figures contain the distribution of PAP observations between time 2 and 3

for Angus (**Figure 3.1**) and Hereford (**Figure 3.2**). Also observed, this variation decreased after bulls are at elevation for a longer period and then returned to moderate elevation. These changes in variation of PAP with age were also observed in study of Neary et al. (2015). Overall, Neary and co-workers suggested that as cattle age and are exposed to high elevation hypoxic environments, the number of extreme high PAP individual observations also increased. This expansion of the right-side of a distribution of PAP bell curve has been documented in previous studies of Angus cattle (Pauling et al., 2018; Cockrum et al., 2019).

Table 3.1. Summary Statistics of Angus Bulls (arithmetic means)

Time	Location	Average Age (d) ± SE	Average Weight (kg) ± SE	N	PAP			
					Mean	SD	Min	Max
1	ARDEC	185 ± 3.9	247.9 ± 5.2	18	38.11	2.49	34	44
2	ARDEC	369 ± 3.9	555.1 ± 9.1	18	41.89	4.83	36	54
3	FLC	424 ± 3.9	-	18	47.28	7.73	38	65
4	FLC	500 ± 3.9	568.8 ± 8.9	18	45.67	6.22	37	57
5	ARDEC	553 ± 3.9	671.5 ± 9.5	18	42.39	2.95	37	49

ARDEC = 1,525 m; FLC = 2,470 m

Table 3.2. Summary Statistics of Hereford Bulls (arithmetic means)

Time	Location	Average Age (d) ± SE	Average Weight (kg) ± SE	N	PAP			
					Mean	SD	Min	Max
1	ARDEC	195 ± 3.9	239.2 ± 9.4	12	37.75	1.06	36	39
2	ARDEC	379 ± 3.9	542.1 ± 11.4	12	39.50	2.65	33	43
3	FLC	434 ± 3.9	-	12	44.33	8.62	39	70
4	FLC	510 ± 3.9	561.0 ± 11.3	12	44.00	5.91	39	60
5	ARDEC	563 ± 3.9	650.8 ± 13.8	12	42.00	4.86	37	54

ARDEC = 1,525 m; FLC = 2,470 m

Body weight and PAP differed ($P < 0.05$) among the 5 time points. Pulmonary arterial pressure also differed ($P < 0.05$) among the breeds at these 5 times. Means of each breed pooled across these times were 41.2 ± 1.3 (Hereford) and 43.2 ± 1.4 (Angus). Pearson correlations (above diagonal) and Spearman's rank correlation (below diagonal) between the fitted values from the regression model are shown in **Table 3.3.** Correlations between yearling PAP (time 2) and PAP measured at a high-altitude times 3 and 4 were highly correlated. The correlations between yearling PAP (2) and PAP at high elevation (2 and 3) were 0.99 and 0.93 respectively. Interestingly, the correlations between the high elevation PAPs and PAP after acclimating again to moderate elevation (time 5) was moderate. The correlation between initial PAP at high altitude (3) and after acclimation (5) was 0.60. The second high elevation PAP (4) was more correlated with after acclimation (5) at 0.77. Historically, weaning PAP has been considered to be less accurate than yearling PAP (Holt & Callan, 2007; Zeng et al., 2016); this current study also supported these findings. The rank correlations presented in the current study yielded similar results. Overall, these estimates provided evidence to help understand how yearling PAP may relate to measures later in life and at differing elevations. However, we must clarify that this study first measured bulls at 1,525 m then at 2,470 m and then again at 1,525 m. Pauling et al. (2018) reported that 1,520 meters was the inflection point where altitude starts to impact hypoxia-induced increases in PAP. Therefore, the altitude of the ARDEC facility of CSU may be high enough to determine if a bull has PAP that will be acceptable or unacceptable for mountainous beef production systems, yet this warrants additional research. The current study also provided additional results of the influences of age-growth on PAP measures. Neary et al. (2015) reported PAP increased with age and weight. The current study involved changes in altitude; therefore altitude, specifically high altitude, yielded increased PAP measurements at those time points (4 and 5).

Table 3.3. Pearson correlations (above diagonal) and Spearman's rank correlations (below diagonal) of predictions for PAP indication of additional PAP measurements

	1^{A}	2^{A}	3^{B}	4^{B}	5^{A}
1^{A}		0.62	0.51	0.50	0.42
2^{A}	0.55		0.99	0.93	0.97
3^{B}	0.48	0.98		0.97	0.60
4^{B}	0.43	0.92	0.97		0.77
5^{A}	0.42	0.63	0.71	0.82	

A = ARDEC (1,525 m); B = FLC (2,470 m)

Implications and Conclusion

This study suggested that yearling PAP was an adequate indicator of future PAP performance in beef bulls. Therefore, these data support the initial research finding that were used in the development of the American Angus Association PAP EPD, which defines the EPD as being a trait of yearling PAP for cattle of high altitude (1,520 m).

This study accomplished the goal of estimating correlations between ages and elevations with PAP. The moderate to strong correlation of moderate elevation yearling PAP with high altitude PAP measurements suggested yearling PAP was a trait indicative of high elevation PAP. Weaning PAP was weakly associated with other measures in this study, therefore, suggesting that it shouldn't be considered indicative of a bull's lifetime PAP, especially if an elevation change is imminent in a bull's future. This study was conducted with a small number of bulls; therefore, it's possible that the correlations will change with additional data. Increasing elevation expanded the average PAP scores and variability of these cattle. As the bull aged, size of the animal also likely increased. Notably, weight was not significant within this model building exercise. This could be due to the potential uniformity within each calf crop. A similar study with larger animal numbers would likely help explain more variability due to weight/size. Age

and elevation appeared to be the most important sources of variation for PAP. Thus, suggesting that the most desirable PAP phenotype is likely a measurement obtained at the altitude at which an animal will reside long-term.

LITERATURE CITED

Angus Genetics, Inc – PAP EPD. 2019. https://www.angus.org/pub/newsroom/Releases/020119-pap-epd-launch.aspx. Accessed February 1, 2020,

Beef Improvement Federation Guidelines. 2020. http://guidelines.beefimprovement.org/index.php/Pulmonary_arterial_pressure_(PAP). Accessed February 1, 2020.

Cockrum, R.R., S.E. Speidel, N.F. Crawford, X. Zeng, H.D. Blackburn, T. Holt, R.M. Enns, M.G. Thomas. 2019.Genotypes identified by genome-wide association analyses influence yearling pulmonary arterial pressure and growth traits in Angus heifers from a high-altitude beef production system. Livestock Science. 224. 75-86. https://doi.org/10.1016/j.livsci.2019.04.004.

Crawford, N. F., M.G. Thomas, T. N. Holt, S. E. Speidel, and R. M. Enns. 2016. Heritabilities and genetic correlations of pulmonary arterial pressure and performance traits in Angus cattle at high altitude. J. Anim. Sci. 94(11), 4483–4490. https://doi.org/10.2527/jas.2016-0703

Gilmour, A. R., B. J. Gogel, B. R. Cullis, and R. Thompson. 2009. ASReml user guide. Release 3.0. Hemel Hempstead (United Kingdom): VSN Int. Ltd

Holt, T. N., and R. J. Callan. 2007. Pulmonary arterial pressure testing for high mountain disease in cattle. Vet. Clin. North Am. Food Anim. Pract 23(3), 575–596. https://doi.org/10.1016/j.cvfa.2007.08.001

Neary, J. M., F. B. Garry, T. N. Holt, M. G. Thomas, and R. M. Enns. 2015. Mean pulmonary arterial pressures in Angus steers increase from cow-calf to feedlot-finishing phases. J. Anim. Sci 93(8), 3854–3861. https://doi.org/10.2527/jas.2015-9048

Pauling R.C., S.E. Speidel, M.G. Thomas, T.N. Holt, R.M. Enns. Evaluation of moderate to high elevation effects on pulmonary arterial pressure measures in Angus cattle1. J Anim Sci. 2018;96(9):3599–3605. doi:10.1093/jas/sky262

Thomas, M.G., J.M. Neary, G.M. Krafsur, T.N. Holt, R.M. Enns, S.E. Speidel, F.B. Garry, A. Canovas, J.F. Medrano, R.D. Brown, and K.R. Stenmark. 2018. Pulmonary hypertension in beef cattle: a complicated threat to health and productivity in multiple beef industry segments. White Paper for Certified Angus Beef. http://www.cabpartners.com/news/research.php. Accepted 5/9/2018.

Zeng, X., M. G. Thomas, R. M. Enns, S. E. Speidel, T. N. Holt. 2016. Angus Cattle at High Altitude: Pulmonary Arterial Pressure, Estimated Breeding Value and Genome-Wide Association Study. Colorado State University. Libraries, Print.

CHAPTER IV

YEARLING PULMONARY ARTERIAL PRESSURE AT MODERATE ELEVATIONS AS A PREDICTOR FOR PULMONARY ARTERIAL PRESSURE AT HIGH ELEVATIONS IN BEEF BULLS IN COLORADO

Summary

High Altitude Disease (HAD) in cattle is a consequence of pulmonary hypertension (PH) induced by hypoxia at elevations > 1,500 m. Pulmonary arterial pressure (PAP) is an indicator of animal susceptibility to PH and HAD and is moderately heritable (h^2 = 0.26 to 0.34). The objective of this study was to determine important sources of variation and to estimate correlation between yearling PAP at moderate altitude and two high altitude PAP measurements. This scenario often occurs in the Western U.S. beef industry. Data consisted of breed, sire, mean PAP (mPAP) measures at each collection date, elevation, and bull age, from 2017 (Angus: n = 19, Hereford: n = 14), 2018 (Angus: n = 19, Hereford: n = 13), and 2019 (Angus: n = 10, Hereford: n = 14) spring-born bulls at the Colorado State University (CSU) Agriculture Research, Development, and Education Center (ARDEC; 1,524 m). A potential 3 PAP measurements were collected from each bull: 1) approximate yearling PAP at ARDEC [2017, 2018, & 2019 bulls]; 2) PAP after acclimating at Fort Lewis College (FLC; 2,470 m), Hesperus, CO [2017, 2018, & 2019 bulls]; and 3) before returning to ARDEC from FLC [2018 & 2019 bulls]. Mean measurement of PAP (mmHg) across the three times were: 40.67 ± 4.17; 43.88 ± 7.69; and 43.74 ± 5.22, respectively. The average age across the times were: 377 ± 15; 419 ± 16; and 490 ± 22 days. In a model development exercise to execute regression analysis, yearling PAP measurement and age were

important ($P < 0.05$) sources of variation. Also, PAP increased ($P < 0.05$) from moderate altitude to high altitude. Specifically, yearling PAP in this model accounted for more variation ($R^2 = 0.53$) in the prediction of the initial high-altitude PAP than it did in the prediction of the second high altitude PAP ($R^2 = 0.35$). Furthermore, yearling PAP measurements collected at 1,525 m were moderately correlated with PAP measures at 2,470 m PAP. Results of this study suggested that the yearling PAP measurement collected at 1,525 m was only a moderate predictor of a PAP measurement collected after 21 days at 2,470 m and these types of predictions weaken after ~ 90 days at high elevation.

Introduction

Pulmonary arterial pressure (PAP) is a phenotypic indicator of pulmonary hypertension (PH) and is used to determine an individual's susceptibility to High Altitude Disease (HAD), a consequence of reduced oxygen from the higher elevations and the potential inefficiencies of the modern bovine cardiopulmonary system. Right-sided heart failure that results from hypoxia at altitudes greater than 1,500 m is a common pathophysiological observation of HAD (Thomas et al., 2018). High altitude disease initiates pulmonary arterial remodeling which ultimately results in death from right-side heart failure. Past research suggests that PAP measurements are moderately heritable, which is important when selecting bulls for high altitude beef production systems (Shirley et al., 2008; Crawford et al.,2016; Pauling et al., 2018; Speidel et al., 2020). High altitude beef production systems produce approximately 1.5 million calves per year. With HAD having an incidence rate of 3-5%, complications from this disease would result in more than 75,000 animals affected (Holt and Callan, 2007; Williams et al., 2012). An issue with utilizing PAP as an indicator of susceptibility to HAD is the reliability based on the varying altitudes where PAP was

initially collected and age of the individual (Pauling et al., 2018; Speidel et al., 2020). The most accurate testing age for PAP is approximately 18 months at an elevation above 1,524 m (Holt and Callan, 2007); however, given the management of most beef production systems, PAP measurements are typically collected prior to 16 months age. Bull and heifer development procedures for most beef production systems typically PAP test cattle at approximately one year of age (culling of animals with measurements > 50 mmHg; BIF, 2020).

The American Angus Association published the first breed-wide expected progeny differences (EPD) for PAP (Pauling et al., 2018; American Angus Association, 2019). Development of EPD with an acceptable accuracy (> 0.4) requires phenotypic information from sires' progeny. There are limited studies of breed differences in PAP (Crawford et al., 2016). The plethora of data needed for a breed conclusion was not possible in these initial studies. Due to the need for data in estimation of EPD, PAP information from moderate and low altitude may be necessitated. The AAA evaluated PAP using data from moderate elevations as a correlated trait to high-elevation PAP EPD (Pauling et al., 2018). This study reported a genetic correlation of 0.83. This was the first study that reported the relationship of PAP at various elevations. An additional study reported similar correlations between data collected at moderate elevations and high elevations (Speidel et al., 2020). Therefore, there is need to learn more about PAP and the sources of variation (breed, age, altitude, sire, etc.) that may influence breeding value estimations. With expected progeny differences (EPD) for PAP measurement becoming available through breed associations, it is important to determine the implications of low to moderate elevation PAP measurements on overall usefulness in estimating high altitude PAP EPD and for the movement of bulls to and(or) from moderate and high elevations.

A portion of the data herein was based from 5 different PAP measurements collected on bulls in 2018 (Chapter III), where dynamics of PAP with changing elevation was observed. This additional study evaluates whether yearling PAP at moderate altitude is predictive of later life PAP measurements at high altitude, and the effectiveness of this measure in predicting PAP measured at a much higher elevation. This study's over-arching goals were to determine if a bull's high-altitude PAP can be predicted by a yearling measurement at moderate elevation using a linear model approach. We are also determining the impact of changing altitude on a bull's PAP measurements, the relationship between PAP at moderate altitude (1,525 m) to PAP at high altitude (2,470 m), and if the time an animal resides at high altitude influences the prediction. An appendix analysis using fattening Angus steers was also included to help understand these types of predictions.

Materials and Methods

This study obtained approval from the Colorado State University Animal Care and Use Committee under protocol number 16-6757AA.

Cattle and Data

Pulmonary arterial pressure was measured on Angus and Hereford bulls (n = 48 and n = 41 respectively) at different ages and elevations as the bulls progressed from yearling to approximately 16 months of age. Cattle were born at an elevation of 1,525 m located at Colorado State University's Agricultural Research, Development, and Education Center (ARDEC) facility in Fort Collins, CO. Bulls used in this study were calved in the spring months ranging from March to May in 2017, 2018, and 2019. Post-weaning, bulls were fed a typical gain test ration targeting 1.5 kg/d. Subsequently, bulls were moved to Fort Lewis College (Hesperus, CO) at an elevation

of 2,470 m from June to August/September 2017, 2018, and 2019 where they grazed irrigated pasture, gaining about 0.5 kg/d. The bulls then returned to ARDEC in September of their respective years. Three mPAP measurements were collected from each bull over this time period: 1) yearling PAP at ARDEC, 2) after acclimating to high altitude (FLC), and 3) before returning to ARDEC from FLC. Bulls were acclimated to each elevation for at least 21 days according to procedure described in Holt and Callan (2007). Each year, there was about 42 days between the yearling PAP observation and the high-altitude PAP observation 1; there was approximately 70 days between high altitude PAP observation 1 and high-altitude PAP observation 2. The total time elapsed between yearling PAP measurement and the final high altitude PAP measurement was 112 days.

Data used in these analyses consisted of breed, mean PAP (mPAP) measures (mm Hg), elevation (m), weight (kg), and age (d). These data are described in Tables **4.1** and **4.2**. All PAP records (n = 234) were collected by T.N. Holt D.V.M (College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO) using procedures described in Holt and Callen (2007).

Statistical Analysis

Model selection was completed using a stepwise regression approach to determine the most important terms to be included in the model. The model utilized for high altitude PAP was as follows:

$$y_i = mu + Age_i + Yearling\ PAP_i + e_i$$

where Age_i was the days in age of the individual bull at high altitude PAP observation, $Yearling\ PAP_i$ was the individual's yearling PAP measurement, and e_i was the residual specific to individuals with observations. The statistical software package of R was used to test differences in high-altitude mPAP within individuals at different ages accounting for the individual's yearling

PAP observation. Fitted values of high-altitude PAP measurements were determined by utilizing regression models in R; consisting of age in days and individual yearling PAP measurments. Yearling PAP fitted values included fixed effect of age in days. Fixed effects included in the analyses consisted of age of each animal at each collection date (in days), yearling PAP at moderate elevation, and breed. Higher orders of the fixed regression for both high-altitude PAP models were considered but did not account for additional variation in PAP ($P > 0.05$). Contemporary groups were considered but did not account for variability in the dependent variable. Contemporary groups were assigned based on birth year. Spearman rank correlations and Pearson correlations for PAP were evaluated from the fitted PAP values.

Pulmonary arterial pressure observations used in this study had a skewed right distribution which parallels reports using similar data (Pauling et al., 2018, Cockrum et al., 2019, Speidel et al. 2020). Figures **4.1** and **4.2** illustrate the right-skewed distribution of data, especially in consideration as altitude and time increases. These figures show the increasing right-skewed distribution in both Angus and Hereford bulls between yearling PAP measurements and high altitude 1 (HA1) PAP measurements. A plot of residuals vs fitted values and a normal quantile-quantile plot were created in R. These plots suggested that raw phenotypes violate assumptions of normality. As a result of the violation, Tukey transformation analysis in R suggested that the raw PAP observations be raised to a power between -3.275 and -6.15 for accommodation of non-normality of data. Resulting parameter estimates of the data transformation were not representative of original observed data scale, and the back transformation was not logical due to nonlinearity between transformed parameter estimates and original data. Due to these issues, models will be presented from an evaluation of raw PAP phenotypes.

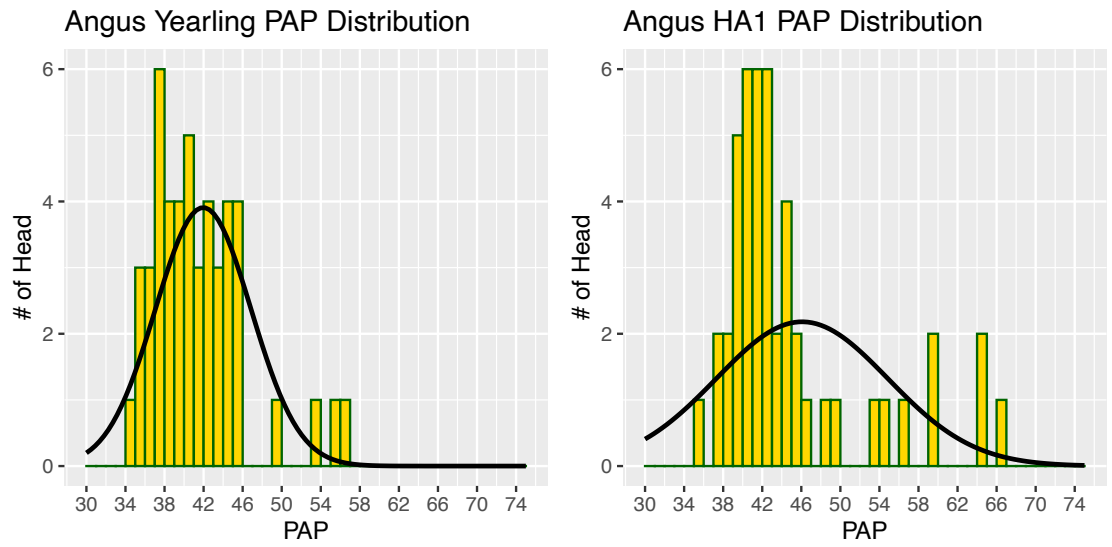

Figure 4.1. Histograms showcasing the increased right-skewed distribution and variation between Angus yearling PAP distribution [left] (elevation = 1,525 m) and Angus high altitude 1 (HA1) [right] (elevation = 2,470 m)

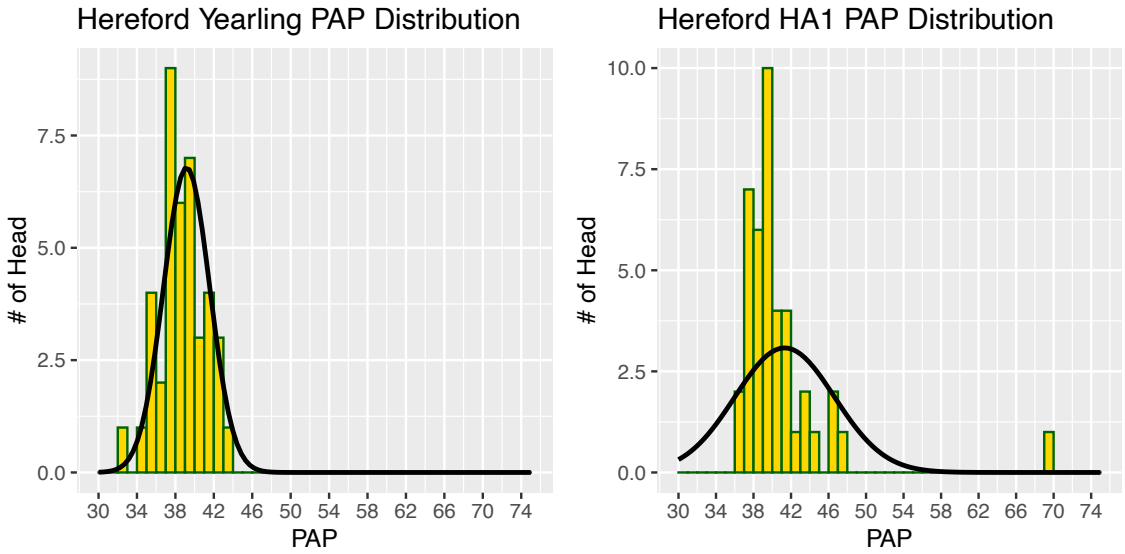

Figure 4.2. Histograms showcasing the increased right-skewed distribution and variation between Hereford yearling PAP distribution [left] (elevation = 1,525 m) and Hereford high altitude 1 (HA1) PAP Distribution [right] (elevation = 2,470 m)

Results and Discussion

Number of observations, arithmetic means, standard deviation (SD), ages, as well as minimum and maximum values for PAP in both Black Angus and Hereford bulls are presented in **Tables 4.1** and **4.2**, respectively. Reduced numbers of observations at time 3 was due to no

collection at that time point for one of the collection years. The most significant model for High Altitude PAP included age in days and the bull's yearling PAP score at moderate altitude ($p < 0.05$) as shown in **Table 4.3**. This table also presents estimates and p-values for the fixed effects on high elevation PAP. The model, which included age in days and yearling PAP, accounted for less variability as the bull spent more time at high altitude than it did for initial high-altitude PAP. This was interpreted because of the reduced partial R^2 values of both yearling PAP and age between the two-model analysis. Yearling PAP as a fixed effect for high-altitude PAP after acclimation (~21 days) had an R^2 value of 0.50, which was reduced to a value of 0.30 after the bulls were at altitude for ~ 90 days. These results illustrate that yearling PAP measurements are highly correlated in the shorter term at higher elevations but as a bull approaches 18 months of age at higher elevations it is less indicative of PAP scores. This result suggested that the genetic mechanisms which influence PAP may be different at moderate elevations than the high elevation genetic mechanisms, as previously described by Speidel et al. (2020). Therefore, making it difficult to know if a bull is tolerating high altitude or PAP changed as a result of failure to adapt.

Table 4.1. Summary Statistics of Angus Bulls (arithmetic means)

Time	Location	Average Age (d) ± SD	N	PAP (mmHg)			
				Mean	SD	Min	Max
1	ARDEC	376 ± 16.11	48	41.96	4.90	35	57
2	FLC	419 ± 15.93	48	46.08	8.78	36	77
3	FLC	490 ± 21.23	27	44.75	5.49	37	57

ARDEC = 1,525 m; FLC = 2,470 m

Table 4.2. Summary Statistics of Hereford Bulls (arithmetic means)

Time	Location	Average Age (d) ± SD	N	PAP (mmHg)			
				Mean	SD	Min	Max
1	ARDEC	377 ± 13.11	40	39.17	2.41	33	44
2	FLC	419 ± 16.23	41	41.36	5.25	37	70
3	FLC	489 ± 23.13	24	42.65	4.77	36	60

ARDEC = 1,525 m; FLC = 2,470 m

Table 4.3. Results of linear model estimates of PAP at 419 ± 16 d (High Altitude 1) and 490 ± 22 d (High Altitude 2) in bulls. Columns include sources of variation, modeled estimate, p-values, and partial coefficients of variations (R^2)

High Altitude 1	Estimate	p-value	Partial R^2
Age 2	0.07758	0.033042	0.05175
Yearling PAP	1.28504	< 0.0001	0.50423

High Altitude 2	Estimate	p-value	Partial R^2
Age 3	0.05569	0.04428	0.07699
Yearling PAP	0.79408	< 0.0001	0.30491

An appendix study involving fattening steers was conducted. We do not know the genetic relationship of high-altitude PH and fattening PAP; however, we know that fattening cattle are hypertensive (Neary et al., 2015; Thomas et al., 2018). Relative to this study we observed that as you move further in time from the initial PAP measurement, the initial PAP is less indicative of later PAP measurements. This was showcased by a reduction in the R^2 values. Adjusted R^2 values were 0.63 for ~3 months post initial PAP and 0.41 for ~6 months post initial PAP measurements. Overall, PAP has been effective in culling extremely hypertensive bulls. However, it is only a moderate tool for assessing lifetime cardiopulmonary fitness.

Figures 4.3 and **4.4** are scatterplots of high-altitude PAP plotted versus the significant model components with a fitted regression line. The positive increasing regression lines indicate the relationships between yearling PAP or age (respectively) and each high-altitude PAP

observation. Also note that within the figures is a boxplot to illustrate the variability of the data and identify outliers common within these types of data (Cockrum et al., 2019). These told us there is a positive relationship between yearling PAP and age and the two high altitude PAP measurements.

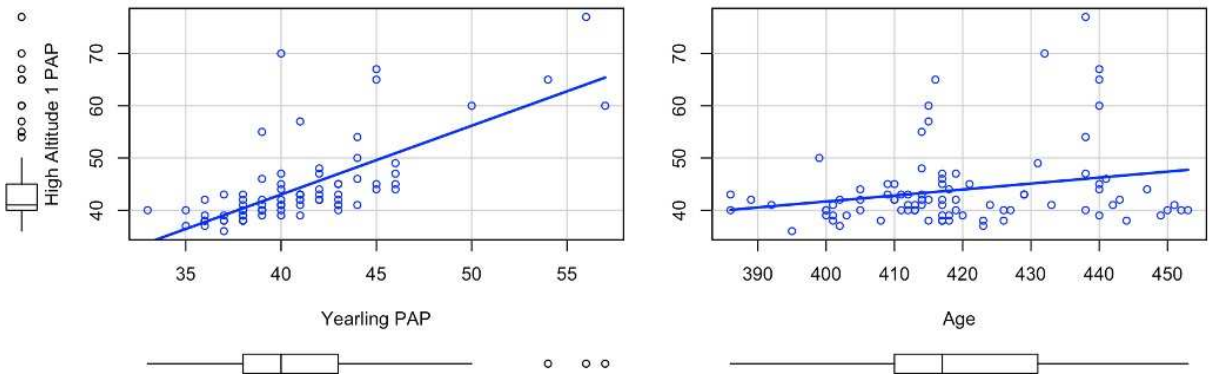

Figure 4.3. Scatterplots and regression lines of raw High Altitude 1 PAP (mmHg) (419 ± 16 d in age after acclimating ~21 days at 2,470 m) and significant model variables (mmHg [left] and days [right]).

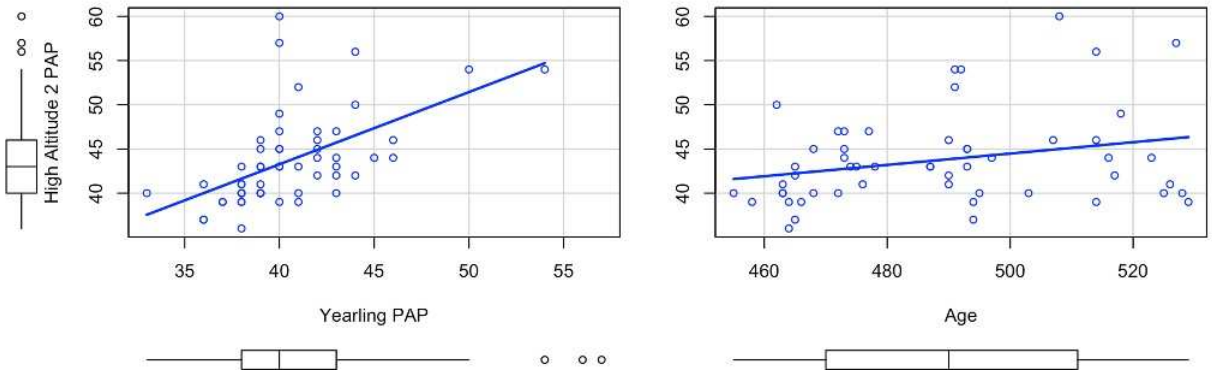

Figure 4.4. Scatterplots and regression lines of raw High Altitude 2 PAP (mmHg) (490 ± 22 d in age after acclimating ~21 days at 2,470 m) and significant model variables (mmHg [left] and days [right]).

Pearson correlations (above diagonal) and Spearman's rank correlations (below diagonal) between the raw PAP values are presented in **Table 4.4.** Correlations between yearling PAP and PAP measured at high altitude were moderately to highly correlated. Estimates (i.e., raw data correlations) between yearling PAP and PAP at high elevation PAP measures 2 and 3 were 0.71 and 0.55, respectively, again suggesting that it is difficult to know if a bull can tolerate high altitude based on the lower (i.e., moderate) elevation PAP. The correlation between the raw PAP measures 2 and 3 at high altitude was 0.81. The magnitude of this correlation suggested that a high-altitude PAP may be a predictor for future PAP measurements at high altitude. Speidel et al. (2020) reported similar behavior in the correlations between the moderate altitude PAP observations and high-altitude PAP observations. These correlations tell us that initial PAP is positively correlated but is a moderate predictor to lifetime PAP. This was illustrated by the decrease in correlation magnitude as time between measurements increases.

Table 4.4. Pearson correlations (above diagonal) and Spearman's rank correlations (below diagonal) of predictions for PAP indication of additional PAP measurements

	1[A]	2[B]	3[B]
1[A]		0.71	0.55
2[B]	0.76		0.81
3[B]	0.63	0.82	

[A] = ARDEC (1,525 m); [B] = FLC (2,470 m)
Ages: 1) 377 ± 15 d; 2) 419 ± 16 d; 3) 490 ± 22 d

Historically, PAP is considered to be the most accurate indicator of an individual's susceptibility to HAD if is measured at high altitude and near 18 months of age (Holt and Callen 2007). These results were supported by this study. However, results also provide evidence to suggest that yearling PAP collected at a moderate altitude is a moderate short-term predictor of PAP at high altitude and leaves uncertainty of the animal's lifetime tolerance of high altitude. The

altitude of the ARDEC facility (1,525 m) of CSU is moderate; therefore, questionable if it yields enough hypoxic stress to determine if a bull has PAP that will be acceptable or unacceptable for lifetime residence in a mountainous beef production system. Therefore, this challenge warrants additional research when considering the diversity of beef operations in the Western US. It was also interesting that early measures in PAP only told us moderate information about lifetime or long-term PAP and were not completely indicative in the long-term. This is an important piece of information as current industry protocol calls for one lifetime PAP measurement. This was illustrated by the reduction in R^2 values and correlations as time progresses in this current study and in the feedlot appendix study.

Implications and Conclusions

This study suggested that yearling PAP at moderate elevations was a moderate and short-term indicator of future PAP performance in beef bulls when moving to high altitudes, and similar measures analyses in feedlot had similar results. Therefore, yearling PAP measurements are likely less indicative of PAP the longer bulls reside at high elevation. It should be noted that high-altitude PAP observations will likely have higher correlations and be a stronger indicator to future high-altitude PAP measures. Breed was not a significant variable in this specific study. This is likely due to limited numbers being evaluated in each breed. To further study breed influence, greater numbers of bulls being analyzed is necessitated. This chapter's results attenuate the somewhat strong conclusion reported in chapter 3 within this study.

LITERATURE CITED

Angus Genetics, Inc – PAP EPD. 2019. https://www.angus.org/pub/newsroom/Releases/020119-pap-epd-launch.aspx. Accessed February 1, 2020,

Beef Improvement Federation Guidelines. 2020. http://guidelines.beefimprovement.org/index.php/Pulmonary_arterial_pressure_(PAP). Accessed February 1, 2020.

Cockrum, R.R., S.E. Speidel, N.F. Crawford, X. Zeng, H.D. Blackburn, T. Holt, R.M. Enns, M.G. Thomas. 2019. Genotypes identified by genome-wide association analyses influence yearling pulmonary arterial pressure and growth traits in Angus heifers from a high-altitude beef production system. Livestock Science. 224. 75-86. https://doi.org/10.1016/j.livsci.2019.04.004.

Crawford, N. F., M.G. Thomas, T. N. Holt, S. E. Speidel, and R. M. Enns. 2016. Heritabilities and genetic correlations of pulmonary arterial pressure and performance traits in Angus cattle at high altitude. J. Anim. Sci. 94(11), 4483–4490. https://doi.org/10.2527/jas.2016-0703

Holt, T. N., and R. J. Callan. 2007. Pulmonary arterial pressure testing for high mountain disease in cattle. Vet. Clin. North Am. Food Anim. Pract 23(3), 575–596. https://doi.org/10.1016/j.cvfa.2007.08.001

Neary, J. M., F. B. Garry, T. N. Holt, M. G. Thomas, and R. M. Enns. 2015. Mean pulmonary arterial pressures in Angus steers increase from cow-calf to feedlot-finishing phases. J. Anim. Sci 93(8), 3854–3861. https://doi.org/10.2527/jas.2015-9048

Pauling RC, Speidel SE, Thomas MG, Holt TN, Enns RM. Evaluation of moderate to high elevation effects on pulmonary arterial pressure measures in Angus cattle1. J Anim Sci. 2018;96(9):3599–3605. doi:10.1093/jas/sky262

Speidel, S.E., M.G. Thomas, T.N. Holt, and R.M. Enns. 2020. Evaluation of the sensitivity of pulmonary arterial pressure to elevation using a reaction norm model in Angus cattle. J. Anim. Sci. 98:1-9. doi:10.1093/jas/skaa129.

Thomas, M.G., J.M. Neary, G.M. Krafsur, T.N. Holt, R.M. Enns, S.E. Speidel, F.B. Garry, A. Canovas, J.F. Medrano, R.D. Brown, and K.R. Stenmark. 2018. Pulmonary hypertension in beef cattle: a complicated threat to health and productivity in multiple beef industry segments. White Paper for Certified Angus Beef. http://www.cabpartners.com/news/research.php. Accepted 5/9/2018.

APPENDIX I: FEEDLOT DATA AND ANALYSIS

PREDICTION OF mPAP IN FATTENING ANGUS STEERS WITH AN EARLY FEEDLOT mPAP MEASURE

As in bulls exposed to high altitude, beef production in Great Plains feedlots appears to also be influenced by pulmonary hypertension (PH; Thomas et al., 2018). Using Angus steers (n = 107; gaining 1.5 kg/day) from a moderate (1,250 m) elevation cow-calf operation with a history of feedlot heart disease, mPAP data was collected after 3, 6, and 9 months of feeding at CSU's Eastern Colorado Research Center (ECRC) and ARDEC. The objective of this study was to use linear regression analyses to evaluate the effectiveness of mPAP collected at 3 months of feeding in predicting mPAP at 6 and 9 months of feeding; therefore, conducting analyses with data from feedlot steers that paralleled the analyses collected from Angus and Hereford bulls described in Chapters 3 and 4. To reiterate, mPAP (mm Hg) was used as an indicator of pulmonary hypertension. These data were from USDA-NIFA project (2018-67015-2824; Metabolism and inflammation predict cardiopulmonary outcomes in fattening beef cattle).

Table A.1 presents summary statistics for weights and mPAP measures from fattening Angus steers. Note the high levels of PH as the steers progressed through the finishing phase. It should also be noted that these cattle were from a study conducting intensive histopathology and transcriptome analyses at harvest, so after 9 months of feeding, only high and low mPAP steers were PAP-tested. **Tables A.2** and **A.3** present results of predictions of mPAP measured at 6 and 9 months of feeding with PAP data collected after 3 months of feeding. Weight and chute order

were fit in these models but were non-significant sources of variation. Pearson correlations (above diagonal) and Spearman's rank correlation (below diagonal) between the mPAP values are presented in **Table A.4**. Correlations between 6 and 9 months of feeding were greater than other correlations. This could be explained by the fact that cardiopulmonary remodeling within the steers had already started taking place. The mPAP from 3 months of feeding predicted ($P < 0.01$) these values at 6 and 9 months of feeding; however, the coefficients of determination and correlations among these traits became less and weaker as time progressed after the sampling at 3 months. In this study, death loss was 5.5% with mortalities attributed to PH-induced heart malformations in the High PAP group. Eighty-six percent of the mortalities occurred after 6 months of feeding. Body weight was similar among the two groups (583 ± 7.3 kg); however, Low PAP steers had better ($P < 0.01$) average daily gain (1.5 > 1.3 ± 0.05 kg/d) and feed efficiency (F:G in kg 2.7 < 3.5 ± 0.2) than High PAP steers (Thomas et al., 2019).

Table A.1. Summary Statistics for fattening Angus Steers

Time	Date	N	PAP (mmHg)				Weight (lbs)			
			Mean	SD	Min	Max	Mean	SD	Min	Max
1	12/10/18	105	44.87	9.38	35	91	757.52	60.83	612	878
2	3/18/19	104	52.17	14.71	38	117	1069.12	83.68	906	1250
3	5/31/19	43	65.12	25.91	38	122	1308.84	73.15	1145	1430

Table A.2 Type III analysis of variance results for factors predicting PAP score after 6 months of fattening

Source of Variation	Estimate	Sum Squared	Degrees of Freedom	F Value	*P*(>F)	Adjusted R^2
(Intercept)	-3.787	60.8	1	0.7605	0.3853	
mPAP (3 months)	1.242	13896.4	1	173.7173	0.0000[a]	0.63
Residuals		7919.4	99			

[a] $P < 0.0001$

Table A.3. Type III analysis of variance results for factors predicting PAP score after 9 months of fattening

Source of Variation	Estimate	Sum Squared	Degrees of Freedom	F Value	*P*(>F)	Adjusted R^2
(Intercept)	-23.591	816.7	1	2.0631	0.1585	
mPAP (3 months)	1.984	11955.8	1	30.2014	0.0000[a]	0.41
Residuals		16230.6	41			

[a] $P < 0.0001$

Table A.4. Pearson correlations (above diagonal) and Spearman's rank correlations (below diagonal) of predictions for PAP indication of additional PAP measurements

	1	2	3
1		0.80	0.87
2	0.62		0.65
3	0.66	0.88	

1 = Initial mPAP at 3 months of fattening
2 = mPAP at 6 months of fattening
3 = mPAP at 9 months of fattening

In conclusion, as Angus steers progressed through the fattening/finishing phase, pulmonary hypertension, measured by mPAP, increased. Also, an early measure of mPAP was an important predictor of later feeding phase mPAPs; however, as time increased between the mPAP measures the amount of variation and Pearson correlations accounted by the initial mPAP measure declined.

LITERATURE CITED

Thomas M.G, J.M. Neary, G.M. Krafsur, T.N. Holt, R.M. Enns, S.E. Speidel, F.B. Garry, A. Canovas, J.F. Medrano, R.D. Brown, and K.R. Stenmark. 2018. Pulmonary hypertension in beef cattle: a complicated threat to health and productivity in multiple beef industry segments. White Paper for Certified Angus Beef. http://www.cabpartners.com/news/research.php. Accepted 5/9/2018.

Thomas M.G., M.M. Culbertson, T. Holt, R.D. Brown, G.M. Krafsur, S.E. Speidel, R.M. Enns, R. Bowen, M. Li, and K. Stenmark. 2019. Metabolism and inflammation predict cardiopulmonary disease outcomes in fattening beef cattle.: Animal Model. 100th Conf. Res. Workers Anim. Disease. P165, Chicago, Ill. November 3-5, 2019.

APPENDIX II: BULL DATA

CALF ID	BREED	HPS	BW	WW	ADJ WW	YW	ADJ YW	ADG	WDA	SC
7105	AN	P	79	440	462	1165		4.24	3.01	37.5
7106	AN	P	68	480	479	1240		4.44	3.20	38.0
7107	AN	P	83	490	489	1265		4.53	3.27	34.0
7108	AN	P	92	660	636	1435		4.53	3.73	37.0
7112	AN	P	69	505	557	1245		4.33	3.28	36.5
7115	AN	P	80	565	625	1325		4.44	3.52	35.0
7116	AN	P	59	405	465	1040		3.71	2.77	33.0
7119	AN	P	82	505	524	1235		4.27	3.37	35.0
7120	AN	P	86	550	594	1370		4.80	3.74	43.0
7121	AN	P	72	480	541	1185		4.12	3.24	35.0
7123	AN	P	65	390	448	1005		3.60	2.75	33.5
7126	AN	P	70	405	426	1065		3.86	2.93	37.5
7127	AN	P	54	490	517	1100		3.57	3.02	36.0
7129	AN	P	76	525	553	1245		4.21	3.42	36.0
7133	AN	P	66	435	526	1195		4.44	3.32	34.5
7134	AN	P	69	370	437	970		3.51	2.70	31.5
7138	AN	P	70	395	498	1110		4.18	3.15	32.5
7140	AN	P	70	415	510	1095		3.98	3.15	34.0
7150	AN	P	90	420	568	1055		3.71	3.17	35.0
8102	AN	P	86	570	583	1245	1170		2.18	38.0
8107	AN	P	65	580	695	1310	1330		2.26	37.5
8109	AN	P	60	520	648	1200	1240	3.78	2.31	37.0
8112	AN	P	80	435	552	1010	1053		2.32	36.0
8115	AN	P	88	470	563	1175	1176		2.50	36.0
8116	AN	P	85	510	627	1170	1201	3.78	2.29	36.5
8117	AN	P	63	535	647	1270	1285	3.65	2.37	35.0
8131	AN	P	74	470	584	1095	1128	3.65	2.33	34.0
8136	AN	P	64	615		1320	1238	3.78	2.15	38.0
8140	AN	P	52	425	502	1055	1109	3.11	2.48	36.0
8141	AN	P	78	420	506	1030	1100	3.11	2.45	37.5
8147	AN	P	95	585	690	1250	1224	4.19	2.14	34.5
8149	AN	P	79	530	636	1200	1218	3.51	2.26	36.5
8152	AN	P	70	560	669	1280	1295	3.11	2.29	36.5
8154	AN	P	74	505	613	1115	1144	2.97	2.21	37.0
8155	AN	P	79	505	633	1180	1220	2.57	2.34	36.5
8156	AN	P	73	440	594	1150	1212	3.24	2.61	35.5
8165	AN	P	68	455	567	1095	1124	3.92	2.41	40.0
8172	AN	P	105	485	589	1140	1159	4.19	2.35	35.5
9107	AN	P	61	655	736	1245			3.28	37.5

9110	AN	P	65	585	669	1100			2.95	34.5
9111	AN	P	78	575	660	1150			2.92	35.0
9113	AN	P	83	605	628	1195			3.10	36.0
9114	AN	P	84	635	662	1240			3.27	35.5
9119	AN	P	86	575	623	1200			3.03	36.5
9125	AN	P	66	560	603	1055			3.01	37.0
9132	AN	P	84	590	669	1170			3.21	34.0
9140	AN	P	92	570	627	1145			3.17	34.5
9144	AN	P	81	580	717	1155			3.28	36.0
7203	HH	H	87	345	392	1000		3.83	2.58	33.0
7213	HH	H	79	370	374	1020		3.80	2.73	34.0
7204	HP	P	85	500	499	1110		3.57	2.87	36.0
7214	HP	P	75	375	439	945		3.33	2.53	33.5
7216	HP	P	61	370	419	1010		3.74	2.73	37.0
7217	HP	P	62	335	383	995		3.86	2.69	31.0
7219	HP	P	65	450	474	1030		3.39	2.83	34.5
7220	HP	P	62	500	527	1065		3.30	2.93	34.0
7222	HP	P	72	450	478	1080		3.68	2.98	36.0
7224	HP	P	92	555	592	1280		4.24	3.55	37.5
7225	HP	P	82	490	525	1125		3.71	3.13	35.0
7230	HP	P	76	400	469	985		3.42	2.74	30.5
7237	HP	P	74	415	454	1080		3.89	3.04	35.5
7244	HP	P	80	425	557	940		3.01	2.82	33.5
8201	HP	P	86	485	599	1105	1138	3.38	2.28	35.5
8203	HP	P	80	445	659	1065	1192		2.39	32.5
8205	HP	P	72	580	593	1260	1209	3.38	2.17	37.5
8207	HP	P	86	570	586	1280	1235	3.11	2.25	38.5
8209	HP	P	83	535	552	1200	1161		2.24	38.0
8215	HP	P	62	575	597	1265	1230	3.65	2.20	39.5
8217	HP	P	71	575	603	1270	1244	3.11	2.21	36.0
8221	HP	P	78	420	486	1100	1138	3.78	2.62	36.0
8223	HP	P	62	440	536	1070	1153	2.97	2.43	34.5
8226	HP	P	85	490	556	1130	1177		2.31	34.5
8228	HP	P	70	440	496	1020	1057	2.43	2.32	35.5
8229	HP	P	82	445	517	1085	1144	2.43	2.44	35.0
8230	HP	P	48	445	510	1095	1148		2.46	32.5
9205	HP	P	83	540	622	1080			2.77	37.5
9206	HP	P	76	565	652	1080			2.90	33.0
9208	HP	P	92	660	692	1170			3.47	39.5
9211	HP	S	110	595	628	1195			3.16	38.0
9216	HP	P	69	555	578	1090			2.97	37.0
9217	HP	P	83	510	561	1095			2.73	32.0
9220	HP	P	80	535	561	1060			2.88	36.0
9222	HP	P	83	575	613	1145			3.11	36.5
9224	HP	P	83	535	636	1165			2.89	34.5

9226	HP	P	75	585	613	1080			3.16	35.5
9257	HP	P	79	530	551	1125			2.74	37.5
9259	HP	P	68	505	567	1005			2.85	35.0
9262	HP	P	98	570	647	1080			3.11	37.0
9263	HP	P	100	470	537	1100			3.06	36.0