THESIS

PULMONARY ARTERIAL PRESSURE IN ANGUS CATTLE: ENVIRONMENTAL INFLUENCES AND RELATIONSHIP WITH GROWTH AND CARCASS TRAITS

Submitted by

Rachel Pauling

Department of Animal Science

In partial fulfillment of the requirements

For the Degree of Master of Science

Colorado State University

Fort Collins, Colorado

Summer 2017

Master's Committee

Advisor: R. Mark Enns

Timothy N. Holt
Scott E. Speidel
Milton G. Thomas

ABSTRACT

PULMONARY ARTERIAL PRESSURE IN ANGUS CATTLE: ENVIRONMENTAL INFLUENCES AND RELATIONSHIP WITH GROWTH AND CARCASS TRAITS

Right-side heart failure (RHF) resulting from hypoxia induced pulmonary hypertension is most commonly observed in cattle located at high elevations, but has been observed in some feedlot cattle residing at low elevations as well. Beef cattle producers typically use pulmonary arterial pressure (PAP) observations to predict an animal's susceptibility to RHF. The objective of this this study was to investigate the effect of elevation on PAP measures, and to evaluate the relationship between PAP, growth traits, and carcass traits in Angus cattle.

The first study utilized PAP and elevation data obtained from the American Angus Association (AAA, n = 4,511), Colorado State University Beef Improvement Center (n = 5,433), and Dr. Timothy Holt DVM (n = 4,821). A univariate analysis of PAP as used to obtain elevation solutions to be input to a polynomial regression to determine high versus low elevation (1,620 m). Then a bi-variate analysis was performed to evaluate the genetic relationship between PAP observations obtained at high elevations as well as low elevations. Results from this study indicate that PAP observations obtained at any elevation can be considered the same trait with a genetic correlation of (0.83 ± 0.15).

The second study utilized data obtained from AAA (n = 4,509) which included PAP, growth, and carcass traits. Multivariate analyses of PAP and growth traits, as well as PAP and carcass ultrasound traits were used to obtain estimates of heritability and genetic correlations. Results from these analyses indicated that there are moderate genetic correlations between PAP

and maternal birth weight (0.55 ± 0.12) as well as PAP and ultrasound ribeye area (0.24 ± 0.12). These results suggested that selection for increased growth and muscling in cattle could consequently increase PAP observations.

ACKNOWLEDGEMENTS

I would first like to express my sincere gratitude to my advisor, Dr. Mark Enns. His guidance and knowledge have contributed to my success at Colorado State University. I would also like to thank my committee members Dr. Timothy Holt, Dr. Scott Speidel, and Dr. Milt Thomas. They were always patient and willing to assist with any problems that I encountered.

Special thanks are also due to my fellow graduate students, Beth Krehbiel, Miranda Culbertson, Natalie Crawford, Ryan Boldt, and Xi Zeng. I learned more in the graduate student office than I did in any classroom, and that is due to the Breeding and Genetics graduate students.

I also would like to express my gratitude to the American Angus Association, the Colorado State University Beef Improvement Center, and Dr. Timothy Holt for providing the data used for this project. This thesis would not have been possible without their contributions.

Finally, I would like to thank my family and friends for their understanding and encouragement throughout my graduate degree. Their reassurance has helped me more than they know.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

Angus is the most commonly used breed of beef cattle in the United States, with more than 300,000 registrations per year (https://www.angus.org/General/gnrlGeneralInfo.aspx). With producer profits being driven by live animal weight and carcass quality, producers have been heavily selecting for improvement in those traits for the last 3 to 4 decades. Figures 1.1 and 1.2 illustrate the genetic trends for growth and carcass expected progeny differences in Angus cattle.

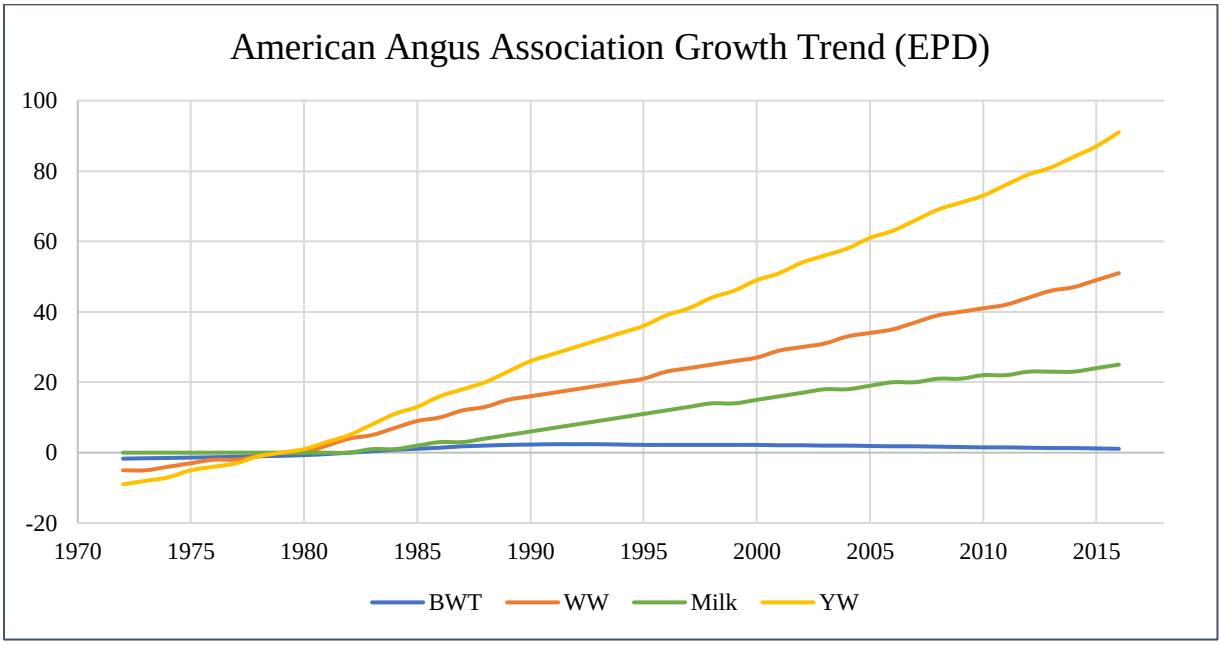

Figure 1.1 Average expected progeny differences in Angus cattle by year for birth weight (BWT), weaning weight (WW), milk, and yearling weight (YW) (http://www.angus.org/Nce/GeneticTrends.aspx).

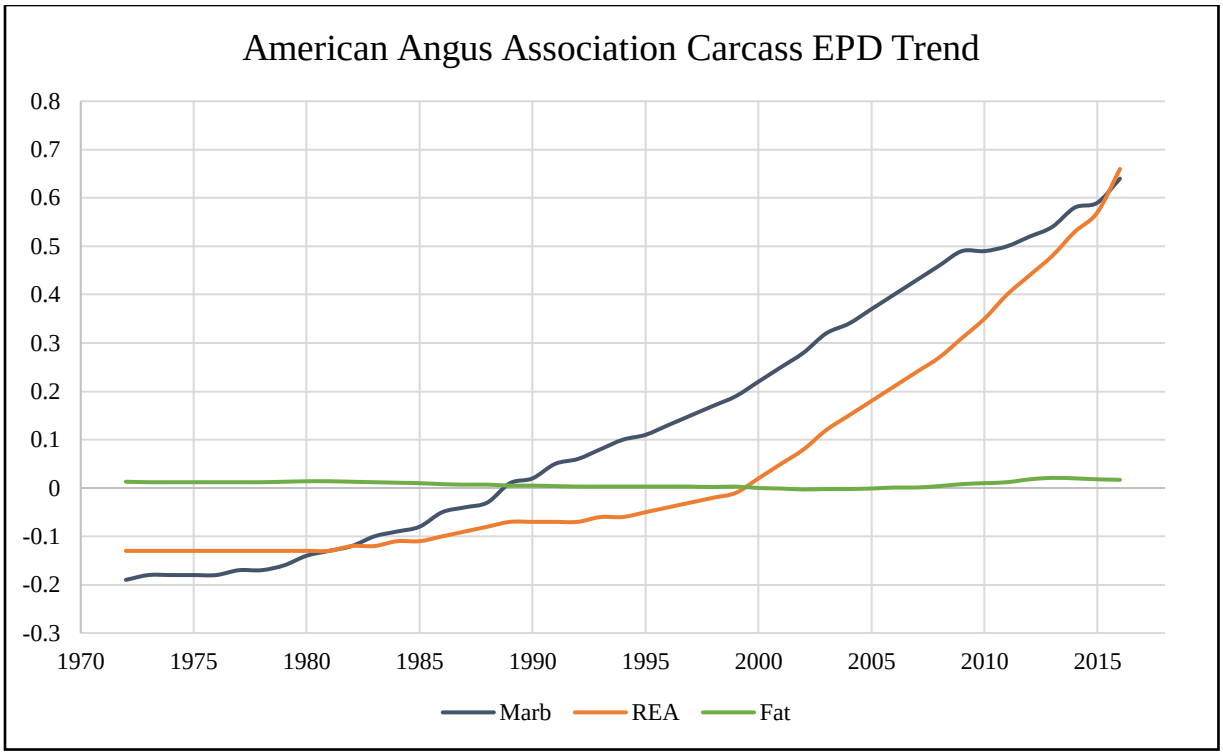

Figure 1.2 Average expected progeny differences in Angus cattle by year for marbling (Marb), ribeye area (REA), and back fat (Fat) (http://www.angus.org/Nce/GeneticTrends.aspx).

While producers located in mountainous regions of the United States are also are driven by the same economic incentives as producers in other regions of the country, their profitability can also be significantly impacted by pulmonary hypertension (**PH**). Historically, PH has been most commonly observed in young calves located at high elevations (Hecht et al, 1962; Holt and Callan; 2007). At high altitude, oxygen diffusion across the alveolar capillary membrane is limited, and this results in an increased alveolar-arterial oxygen tension difference (Des Jardin, 2002), consequently causing cardiac output to increase. Prolonged periods of increased cardiac output will eventually cause pulmonary vasoconstriction, and subsequent right-side heart failure (**RHF**) (Humbert et al., 2004). Approximately 5 % of total calf death losses in high altitude regions (> 1,500 m) can be attributed to hypoxia induced RHF (Holt and Callan, 2007).

Pulmonary arterial pressure (**PAP**) can be used to confirm the presence and degree of PH (Holt and Callan, 2007). Beef producers at high elevations (>1,500 m) have been using PAP observations to determine which animals are most at risk for PH. Currently, these observations are only considered reliable when they are obtained above 1,500 m (Holt and Callan, 2007). This requirement typically limits the outside genetic resources that high elevation beef cattle producers can utilize with confidence, because progeny performance from sires located at low altitude can be unpredictable for PAP and at risk of PH. Investigating the relationship between PAP and elevation could help quantify the value of PAP observations obtained at low elevations.

Cattle are more susceptible to the effects of hypoxia than similar livestock species due to smaller lung capacity and greater metabolic oxygen requirements (Viet and Farrell, 1978). At rest the bovine cardiopulmonary system is working at maximum capacity, consequently making cattle particularly susceptible to cardiac and respiratory diseases (Neary et al., 2013). In addition to elevation, it has been hypothesized that increased growth and fat deposition may contribute to increased cardiac output and elevated PAP (Jensen et al., 1976, Neary et al., 2015). Since there has been a dramatic increase in growth and carcass characteristics in Angus cattle for several decades, it is critical to evaluate the genetic relationship between those traits and PAP.

The objectives of this thesis are to:

1. Evaluate the relationship between PAP taken at various elevations and thereby determine the value of PAP observations obtained at low elevations.
2. Evaluate the relationship between PAP and growth traits in Angus cattle.
3. Evaluate the relationship between PAP and ultrasound carcass traits in Angus cattle.

LITERATURE CITED

American Angus Association (AAA). 2016. Genetic trend EPD and $value by birth year. http://www.angus.org/Nce/GeneticTrends. aspx. (Accessed 4 December 2016).

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

Hecht, H. H., H. Kuida, R. L. Lange, J. L. Thorne, and A. M. Brown. 1962. Brisket disease: II. Clinical features and hemodynamic observations in altitude-dependent right heart failure of cattle. Am. J. Med. 32:171-183.

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.

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.

Neary, J. M., D. H. Gould, F. B. Garry, A. P. Knight, D. A. Dargatz, and T. N. Holt. 2013. 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., 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.

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.

CHAPTER 2

REVIEW OF LITERATURE

In 1915, Glover and Newsom reported a disease in cattle located at high elevations in Colorado. The most common symptom of the disease was edema in the animal's brisket region. In addition to the swollen brisket, most animals also showed signs of lethargy, cough, and heavy breathing. Animals experiencing these symptoms typically died between 2 weeks to 3 months after symptom development.

Glover and Newsom (1915) investigated the disease characteristics including transmission, manifestations, and potential remedies. The condition was ultimately termed "brisket disease", and was determined to be non-transmittable with occurrences in cattle located at high elevations only. The authors stated that the cause was likely due to lack of acclimatization to extreme altitudes, ultimately resulting in exhaustion of the heart. They concluded that the only treatment for animals developing brisket disease relocation to lower elevations.

Hecht et al. (1962) sought to evaluate the cardiovascular systems of cattle that had been living at high elevations using calves suffering from acute brisket disease as well as healthy calves. The authors concluded that "brisket" animals suffered from striking increases in pulmonary artery pressure due to excessive increases in pulmonary arteriolar resistance, commonly known as pulmonary arterial hypertension (**PH**). Ultimately PH would lead to right-side heart failure (**RHF**) due to the overload of the right ventricle.

Initially, brisket disease was thought to only occur at extreme elevations above 2,134 m (Glover and Newsom, 1915). However, more recently Holt and Callan (2007) reported

occurrences of brisket disease above elevations of 1,524 m. Jensen et al. (1976) reported incidences of RHF in feedlot cattle located at an altitude of 1,600 m. More recently, RHF was found to be the second leading cause of death in a group of dairy heifers, also located at 1,600 m (Malherbe et al., 2012). While considered to be a disease isolated to high altitude regions, a recent report by Neary et al. (2016) suggested that brisket disease is no longer unique to high altitude. Through a survey of 15 feedlots, the authors reported that the incidence of RHF has been increasing in feedlot cattle since 2000, indicating that death loss due to RHF is a concern to the entire beef industry, not just beef producers located at high elevations.

SECTION 1: RIGHT-SIDED HEART FAILURE DUE TO PULMONARY HYPERTENSION IN BEEF CATTLE

Physiology of Pulmonary Hypertension

Veit and Farrell (1978) demonstrated that beef cattle have a small gaseous exchange capacity relative to their basal oxygen need when compared to other mammals. Compared to horses, cattle have approximately one third of the lung capacity and nearly two and a half times the oxygen requirements. Selection in cattle for greater digestive capacity, muscle mass, milk production, and growth rate collectively increases total body metabolic oxygen requirements relative to the anatomical pulmonary gaseous exchange capability**.** Modern cattle have small lungs relative to their body size and metabolic demands, making them more susceptible to cardiopulmonary disease (Neary et al., 2013a).

Pulmonary arterial hypertension is a disease that originates in the pulmonary arteries within the lungs of an animal, and is characterized by elevated pulmonary arterial pressure

(**PAP**) (Chin et al., 2008). When left untreated PH can lead to RHF and death. Under hypoxic conditions, a morphological change known as medial muscular hypertrophy occurs in the small pulmonary arteries and arterioles causing increased resistance to natural blood flow (LeValley, 1978). Since cattle have an unusually muscular pulmonary vasculature, they are particularly susceptible to hypoxic pulmonary vasoconstriction (Heath et al., 1984), which could ultimately lead to PH and RHF. Conditions that may induce 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). Figure 2.1 illustrates changes in blood flow and resistance due to pulmonary artery stiffening.

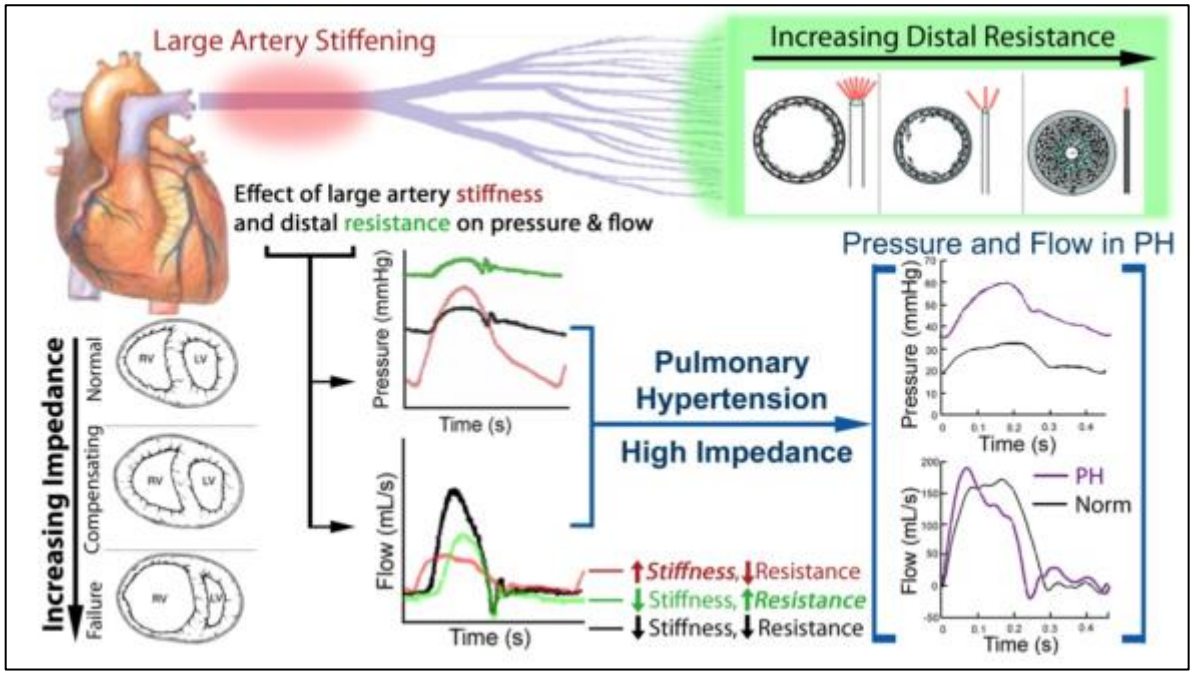

Figure 2.1. Diagram demonstrating the relationship between ventricular work, impedance to flow due to large pulmonary artery stiffening and resistance to flow due to narrowing of the distal pulmonary vessels. Vascular stiffness, due to structure-function changes in vessel wall elastin, and distal resistance,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

Pulmonary Arterial Pressure Testing

Background

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 be retained as breeding animals for herds located at altitudes greater than 1,524 m. Table 2.1 illustrates different classifications of PAP observations and the interpretation of those classifications.

Table 2.1 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 41 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).

Pulmonary arterial pressure testing is currently the best tool to help producers select cattle that are less susceptible to the development of PH. Producers have been utilizing PAP tests for over 40 years to help make selection decisions in their herd, but after decades of selection some herds located at higher elevations still experience death loss due to PH. It is not completely understood why death loss is still occurring in these herds, however, Neary et al. (2013a) speculated that PAP measurement and screening cannot, by itself, eliminate the occurrence of PH if the disease is not solely attributable to alveolar hypoxia.

Pulmonary Arterial Pressure Collection

The PAP collection procedure involves passing flexible catheter tubing through a large bore needle inserted into the jugular vein. Due to the invasive nature of this procedure, the animal being tested must be properly restrained with head and neck movement impeded. Once the animal is properly restrained, a catheter is passed through the bore needle, down the jugular vein, through the right atrium, into the right ventricle, and into the pulmonary artery. A pressure transducer located at the end of the catheter measures systolic and diastolic pressures, which are used to calculate a mean PAP measurement. A trained veterinarian will monitor the pressure changes and characteristics displayed on a blood pressure monitor to determine location of the pressure transducer within the animal's cardiovascular system. In cattle, blood pressure should be between 6 to 12 mmHg in the jugular vein and right atrium, 18 to 30 mmHg in the right ventricle, and 34 to 44 in the pulmonary artery (Holt and Callan, 2007). Figure 2.2 illustrates the changes in blood pressure wave characteristics as the pressure transducer moves through the heart.

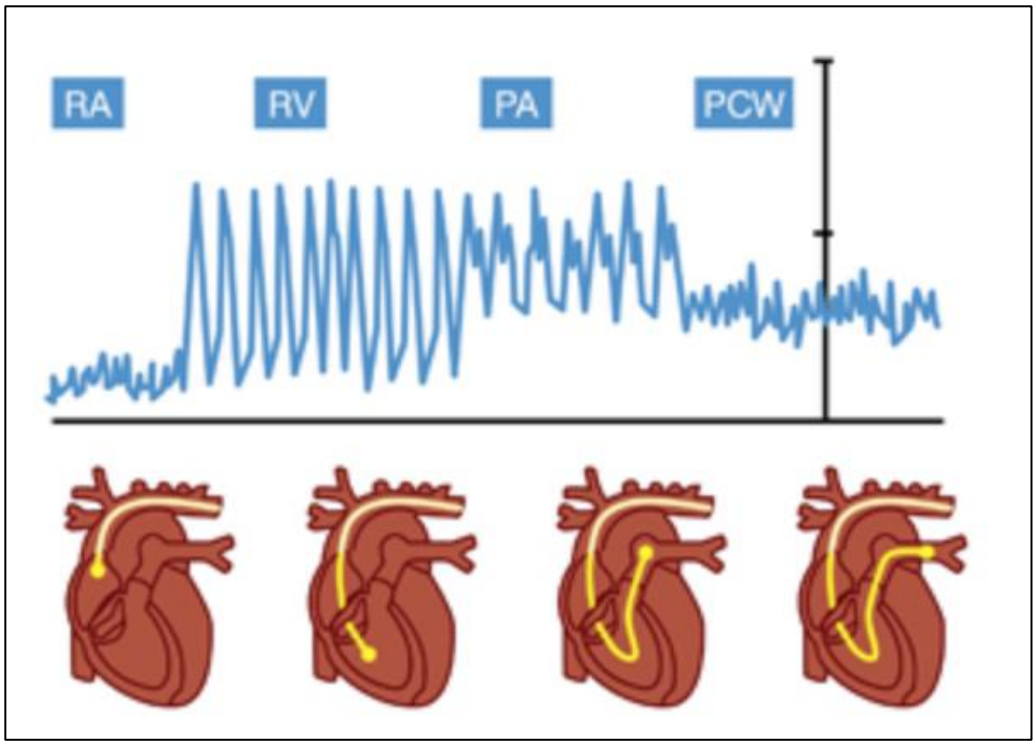

Figure 2.2 Characteristic intracardiac pressure waveforms during passage through the right atrium (RA), right ventricle (RV), pulmonary artery (PA), and pulmonary capillary wedge (PCW) (http://www.pah-info.com/Image-gallery#)

Alternative to Pulmonary Arterial Pressure Testing

Pulmonary arterial pressure testing is an invasive procedure that can be time consuming and costly to beef cattle producers. Many producers at lower elevations do not utilize PAP testing in their herds because their cattle are not commonly affected by PH, and PAP observations obtained at low elevations are not typically accurate in predicting an animal's susceptibility to PH. Ahola et al. (2006) attempted to identify possible alternatives to PAP testing that would be cheaper and easier to collect. The authors sought to determine if there was a relationship between PAP observations and blood components obtained from 3 different blood evaluation technologies: hemogram, pulse oximetry, and a portable clinical analyzer. The hemogram and portable clinical analyzer are both typically used to evaluate blood component

characteristics. The portable clinical analyzer can be used to evaluate blood in the field, while the hemogram is only used in a laboratory. Pulse oximetry was also utilized to evaluate blood oxygen levels. Blood components evaluated using pulse oximetry and the portable clinical analyzer were not found to be significant. The hemogram utilized whole blood to evaluate 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 count, mean corpuscular hemoglobin, and mean platelet volume. Pearson correlation coefficient results showed moderate correlations between PAP observations and PCV (r = 0.31), HgB (r = 0.33), and RDW (r = -0.36). A stepwise model selection was utilized to determine hemogram factors to be included in a multiple regression analysis. Hemoglobin concentration and RDW were used in a multiple regression analysis, where the resulting R^2 was only moderate (0.305), indicating that these two factors only explain approximately 31 % of the variability in PAP observations. Therefore, PAP testing is still the best option available to producers to determine if an animal is susceptible to developing PH.

Influences on Pulmonary Arterial Pressure

Breed

Research by Crawford (2015) evaluated breed differences for PAP in over 2000 bulls present in the 4-corners bull test (Hesperus, CO) between 1983 and 2005. Crawford ultimately found that Angus-Gelbvieh cross cattle had the lowest mean PAP and Simmental cattle had the highest mean PAP observations, when compared to Angus, Charolais, Gelbvieh, Hereford, Limousin, Maine Anjou, Red Angus, and Saler bulls. Holt and Callan (2007) reported

incidences of high PAP values in nearly every breed of cattle with PAP observations; illustrating that no specific breed of domestic cattle are immune to the effects of hypoxia.

Other members of the cattle family, such as the yak, have adapted to living in the high altitude of the Himalayan mountains, and through the course of evolution, lost the property of hypoxic pulmonary vasoconstriction (Heath et al., 1984). Unlike the yak, today's cattle populations have not resulted from natural selection in high altitude environments, but rather from artificial selection. With advances in reproductive technologies, cattle producers have the ability to utilize genetic resources from all over the world. While this ability allows producers to make rapid genetic improvement in various performance traits, it could potentially slow genetic improvement in various health traits associated with different production environments.

Gender

Several studies have shown a significant difference in PAP observations between sexes. Rabinovitch et al. (1981) found that female adult rats were significantly less hypertensive than males. The authors speculated that this was because females have fewer muscularized alveolar wall arteries than males. A genetic evaluation of PAP in Angus cattle raised at high elevation (2,170 m) described by Cockrum et al. (2014) reported that the heritability of PAP was a different between heifers and bulls at 0.21 ± 0.04 and 0.38 ± 0.08 respectively, with a genetic correlation of 0.64 ± 0.14, indicating that PAP can be considered a different trait when measured in different sexes. Both studies indicate PH may be influenced by hormonal differences. However, Holt and Callan (2007) claimed that there is no physiological basis for a difference in PAP measurements

between sexes in cattle, and any differences that are seen are likely due to differential management of the sexes.

Age

Response to hypoxia is affected by age, particularly in young animals. The lungs of young animals are not fully mature and are therefore more susceptible to the effects of hypoxia (Stenmark et al., 2009). A study on infant rats under hypoxic conditions showed that as lung volume increased, alveoli in the lungs did not multiply normally, indicating that vascular remodeling which resulted from hypoxia did not permit normal alveolar multiplication, thereby, decreasing total alveolar surface area in the lung, in turn decreasing the animal's ability to utilize available oxygen (Rabinovitch et al., 1981). Holt and Callan (2007) stated that PAP testing cattle at 16 months or older is most accurate, however, as an animal ages, the mean PAP measurement increases. Enns et al, (1992) reported that PAP observations in an Angus herd located at an elevation of 2,070 m increased by 0.0387 mmHG per day of age. This is likely due to the natural stiffening of the blood vessels as an animal ages (Lam et al., 2009).

Concurrent illness

High intrapulmonary arterial pressures exist in a variety of disease conditions, including mitral stenosis, some congenital heart diseases, recurrent pulmonary embolism, primary parenchymal disease of the lung, and idiopathic or primary pulmonary hypertension (Alexander and Jensen, 1963). Viral, bacterial, and even parasite infections can also predispose animals to

pulmonary hypertension, therefore, PAP observations from sick animals should not be considered reliable (Holt and Callan, 2007).

Environmental Conditions

Environmental cold temperatures have been shown to cause an increase in PAP and vascular resistance and a fall in arterial oxygen tension (Will et al., 1978). Cattle exposed to temperatures below 0°C for at least 48 h had increased PAP measurements at levels between 25-55%. After the 48 h period, cattle were supplemented oxygen and their PAP measurements returned to their original levels. The response to supplemental oxygen indicates that the increase in pressure was due to the increased pulmonary blood flow during periods of cold exposure.

Elevation

Historically, elevation has been the biggest environmental influence on PAP. Holt and Callan (2007) stated that the hypoxic conditions needed to stimulate a pulmonary response are not seen until approximately 1,524 m. As an individual moves up in elevation, the degree of pulmonary vasoconstriction and hypertension also increases (Des Jardin, 2002). Holt and Callan (2007) reported an increase of 1-2 mm Hg in PAP observations for every 305-meter increase in elevation above 1,524 m. Since an individual's PAP observation changes as elevation changes, only PAP observations obtained at elevations greater than 1,524 m should be considered a reliable predictor for an animal's susceptibility to developing PH due to elevation. Cattle should also be located at that elevation for at least 3 weeks prior to testing in order for their bodies to acclimate appropriately (Holt and Callan, 2007).

Clinical signs and symptoms of bovine pulmonary hypertension

The most common sign that an animal is experiencing PH is a noticeable swelling or edema in the brisket region. Edema is a result of increased hydrostatic pressure due to right ventricle cardiac failure and venous hypertension (Holt and Callan, 2007). Congestive heart failure causes water in the blood vessels to pool in the thoracic and abdominal cavities of an animal due to the loose nature of tissue and hide (Hecht et al., 1962; Neary et al., 2015). Cattle typically show signs of rapid heavy breathing, dull expression, lethargy, fever, diarrhea, jugular distension, and drooped ears prior to the development of edema (Holt and Callan, 2007; Neary et al., 2013a). However, these symptoms can commonly be confused for symptoms of pneumonia, and are often misdiagnosed.

SECTION 2: PREVALENCE OF PULMONARY HYPERTENSION IN THE BEEF INDUSTRY

Approximately 1.5 million cattle in the United States are raised at high altitude (>1,524 m) with 5 percent of total annual death losses in these areas attributed to PH induced RHF (Holt and Callan, 2007). There are examples of beef cattle ranches that have experienced death loss at much higher rates. Holt and Callan (2007) reported an incident where a Colorado ranch experienced a 25 percent loss in yearling cattle in a single year. While cattle at high elevation comprise a relatively small percentage of total US beef cattle numbers (93,584,600; USDA-ARS, 2017), PH can have a huge economic impact on producers located at high elevations.

A survey of 5 ranches located at high altitude showed that half of total necropsied calves (n = 28) between 6 weeks and 7 months of age had lesions consistent with PH and the other half

had lesions consistent with pneumonia (Neary et al., 2013a). The ranches surveyed had been utilizing bulls with low PAP observations for 20 years, yet half of their calf death loss was due to RHF secondary to PH. Neary also stated that this might be because PAP measurements and screening cannot, by itself, eliminate the occurrence of PH if the disease is not solely attributable to alveolar hypoxia.

Originally, it was thought that hypoxia induced PH primarily affected young calves at extreme elevations (> 2,500 m); however, more recently, brisket disease has been observed in feedlot cattle as well. This was first reported in feedlot cattle located at 1,600 m (Jensen et al., 1976). It was found that 116 out of 1,988 animals that were necropsied had suffered from RHF secondary to PH. Jensen proposed that the occurrence of PH in feedlot cattle could be caused by: high genetic susceptibility, origin from mountains, rapid growth rates, and hypoventilation. At the time of that study, feedlot cattle had an average daily gain between 1 and 1.5 kg, leading the authors to postulate that the rapid growth rates could cause an animal's cardiopulmonary system to dramatically increase output. Jensen also proposed that hypoventilation, due to intra-abdominal pressure, could result in airway hypoxia and ultimately heart failure. Fifty animals in the study observed to have developed brisket disease, also showed signs of pneumonia which could contribute to airway hypoxia.

In a study conducted on Holstein heifers at a Colorado dairy located at an elevation of 1,600 m, RHF secondary to right ventricular hypertrophy was observed to be the second leading cause of death (Malherbe et al., 2012). The dairy reported that death-loss due to RHF accounted for approximately 22 percent of total heifer deaths over a 7-year period. Clinical details were reported on 10 heifers that were determined to be affected by RHF. These animals died at

varying ages and seasons, with 7 of the 10 heifers having been treated for pneumonia prior to death.

A survey of North American Feedlot cattle sought to identify the risk of RHF over a 12-year period (Neary et al., 2016). Canadian feedlots (n = 10) were surveyed once every 4 years from 2000 to 2012. Likewise, 5 feedlots in the United States were surveyed in 2012 only. All the feedlots surveyed maintained health records on every animal and performed necropsies on all mortalities. While total death loss due to RHF was significantly lower (75-80 % lower) than death loss due to digestive disorders, the relative risk of RHF in Canadian feedlot cattle doubled from 2000 to 2012. Cattle treated for bovine respiratory disease were 2 to 3 times more likely to die from right-sided heart failure. Approximately half of the heart failure cases reported occurred after 19 weeks from feedlot entry, making those losses extremely expensive to the feedlot.

Recent research has shown that congestive heart failure has become problematic in feedlot cattle in the late stages of the finishing phase. This is likely due to high mean PAP throughout the feeding period (Neary et al., 2015). To further evaluate this hypothesis, the authors collected PAP observations on a group of male calves from 4 to 18 months of age. These calves were born and raised on a ranch with an average elevation of 2,170 m. After weaning, the calves were moved to lower elevations. Animals were PAP tested 4 times between 4 and 18 months of age, with 2 PAP observations obtained at high elevation (2,170 m), and 2 PAP observations obtained at lower elevations (1,560 m or 1,300 m). The authors reported that mean PAP observations increased throughout the feeding period, and animals that had the highest PAP observations as calves also had the highest PAP observations through the testing period. Table 2.2 presents mean PAP observations from each age range. Increased mean PAP

through the feeding period could be amplified by body fat accumulation and ruminal engorgement that occurs in late stage feedlot cattle (Jensen et al, 1976). Ruminal engorgement could cause increased intra-abdominal pressure, and prevent the animal from utilizing its full lung capacity which could lead to hypoxia induced PH. Neary stated that body fat accumulation may predispose cattle to higher systolic PAP and arteriolar wedge pressures which can contribute to increased mean PAP and cardiac dysfunction.

Table 2.2. Adjusted cell means and 95 % confidence intervals for mean pulmonary arterial pressures in clinically healthy nonimplanted, Angus steers according to age (mo). Adapted from Neary et al., 2015

Age [1], mo	Mean pulmonary arterial pressure, mm Hg
4	38.6[a] (32.5 to 44.6)
6	41.7[a] (35.7 to 47.8)
13 (A)	40.9[a] (38.8 to 42.9)
13 (B)	43.3[a] (41.2 to 45.3)
18	50.3[b] (48.2 to 52.4)

[a,b] Values without a common superscript differ ($P < 0.05$). Type 1 error = 0.05.
[1] A = 13 mo steers tested in Fort Collins, CO; B = 13 mo steers tested in Akron, CO.

SECTION 3: GENETIC EVALUATIONS OF PULMONARY HYPERTENSION IN BEEF CATTLE

Quantitative Genetic Evaluations of Pulmonary Arterial Pressure

Will et al. (1975) suggested the magnitude of pulmonary vascular responses to hypoxia were genetically influenced. At the time of that study, it was unclear the magnitude of that influence. Historically, management of disease focused on modifying the animals' environment, with little attention given to the potential for genetic improvement of health-related traits.

Incidence of PH and RHF in a beef cattle herd is difficult to determine because proper diagnosis of affected animals is challenging in a range environment. Due to this challenge PAP measures are used as an indicator trait to determine an animal's susceptibility to PH. As previously stated by Holt and Callan (2007), PAP measurements are only accurate when made at elevations greater than 1,524 m, and only when animals are at that elevation for at least 3 weeks. As a result, cattle producers that raise animals at lower altitudes do not typically collect PAP observations because there is little economic incentive. Enns et al. (2011) stated that this limitation creates a need for the development of indicator traits genetically correlated to the trait of interest.

Extensive research has been conducted at Colorado State University to evaluate the genetic variability of PAP and genetically correlated traits. This research has shown that PAP is moderate to highly heritable (0.20 – 0.77) in Angus and Hereford cattle, suggesting that selection for decreased PAP observations in replacement animals can lead to lowered PAP observations in their progeny. Table 2.3 describes previously reported PAP heritability estimates obtained from Angus and Hereford cattle.

Table 2.3. Pulmonary arterial pressure heritability estimates (SE) previously reported.

Reference	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 (2016)	0.26 (0.03)	-	-	-	Angus

[1] Heritability estimate obtained from bulls, heifers, and steers combined
[2] Estimate for first pulmonary arterial pressure taken
[3] Estimate for second pulmonary arterial pressure taken
[4] Estimate for third pulmonary arterial pressure taken

Initial heritability estimates of PAP were moderate to high (LeValley, 1978; Schimmel,1981; Enns et al, 1992), while estimates made in the last decade are low to moderate (Shirley et al, 2008; Cockrum et al, 2014; Zeng et al., 2014; Crawford et al, 2016). Heritability estimates obtained by Cockrum, Zeng, and Crawford were obtained using data from the Colorado State University Beef Improvement Center. Cockrum and Zeng utilized yearling PAP observations, while Crawford utilized weaning PAP observations.

Enns et al. (2011) calculated PAP expected progeny differences (**EPD**) for the Colorado State University Beef Improvement Center (Saratoga, WY; 2,170 m) as well as the Tybar Ranch (Carbondale, CO; 1,880 m). These EPDs were used as selection criteria in both herds, and the implementation of the PAP EPD led to a downward trend in the average PAP EPD values in both herds (Figure 2.3). While research has shown that selection for decreased PAP observations can be successful, producers still report death loss in their calf crop due to PH. This is likely due to the use of outside sires through artificial insemination (**AI**). Many AI sires are not reared at high

elevations and therefore do not have a PAP observation, making their progeny performance hard to predict at high elevations.

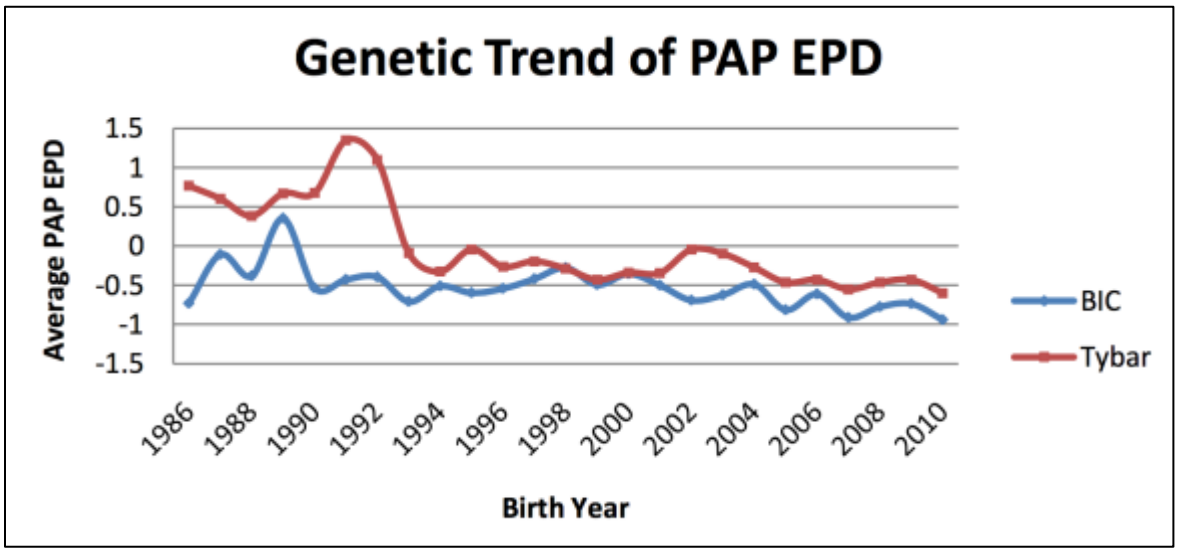

Figure 2.3. Genetic trend in pulmonary artery prssure at the Tybar Ranch (Tybar) and the Colorado State University Beef Improvement Center (CSU-BIC) since selection with EPD began in 1992 (Tybar) and 2002 (CSU-BIC) (Enns et al., 2011).

It has been hypothesized that high growth rates in cattle could contribute to increased PAP observations (Jensen et al., 1976; Viet and Farrell, 1978; Neary et al., 2015). Shirley et al. (2008) stated that direct effects for weaning weight and yearling weight in Angus cattle have been steadily increasing over the last 3 decades at 1.5 and 2.8 kg per year making estimating the strength of the genetic relationship between these traits and PAP essential. Table 2.4 provides genetic correlation estimates for various growth traits and PAP from previously reported studies. While all the previous studies reporting genetic correlations with PAP utilized data from Angus cattle, there were still significant differences in estimates. Computing power at the time of Schimmel's (1982) research was likely not as powerful as that of Shirley et al (2008) and Crawford et al (2016), so those estimates may not be as reliable. Shirley et al (2008) and

Crawford et al. (2016) both estimated a moderate genetic correlation between PAP and weaning weight direct in Angus cattle. Both authors reported a positive genetic relationship between PAP and birth weight direct, but the magnitude of the relationship was much different. This was likely due to a difference in the sample populations.

Table 2.4 Genetic correlations estimates (SE) between pulmonary arterial pressure and growth traits previously reported

	Reference		
Trait	Schimmel (1982) [1]	Shirley et al. (2008) [1]	Crawford (2016) [2]
Birth Weight Direct	-0.43 (0.29)	0.49 (0.12)	0.15 (0.09)
Birth Weight Maternal	-	0.01 (0.17)	0.14 (0.10)
Weaning Weight Direct	0.19 (0.34)	0.51 (0.18)	0.22 (0.08)
Weaning Weight Maternal	-	-0.05 (0.14)	-0.03 (0.08)
Yearling Weight Direct	-0.75 (0.65)	-	0.12 (0.08)
Yearling Weight Maternal	-	-	0.00 (0.09)
Post-weaning Gain	-	-	-0.10 (0.10)

[1] Pulmonary arterial pressure measurements obtained at weaning
[2] Pulmonary arterial pressure measurements obtained at yearling

Molecular Genetic Evaluations of Pulmonary Arterial Pressure

Few studies evaluating hypoxia-induced PH from a molecular genetic standpoint have been reported in literature for cattle. A small study took DNA and RNA samples from 20 Angus cattle raised at an elevation of 2,590 m, where 10 animals were considered hypertensive and the other were considered normal (Newman et al., 2011). The authors utilized a SNP array in a genome wide association study to identify gene differences among the hypertensive and normal cattle. From the SNP array, three genes were identified; myosin heavy chain 15 (**MYH15**), NADH dehydrogenase flavoprotein 2 (**NDUFV2**), and FK binding protein 1A (**FKBP1A**). However, none of these genes were found to be significantly associated with mean PAP in the cattle studied. A follow up study re-evaluated the association of the 3 previously mentioned genes with mean PAP (Neary et al., 2014). This study sampled Angus bulls residing at 2,182 m,

as well as a small group of Yaks residing at 1,500 m. They concluded that a T allele variant in the MYH15 gene was significantly associated with low PAP observations in cattle. All Yaks sampled were homozygous for the same T allele of the MYH15 gene. As previously stated Yaks are part of the same family as cattle, however, they are better adapted to high altitudes. This is likely due to generations of natural selection in its native mountainous regions of Asia. The authors stated that the association between the T allele polymorphism and hypoxic disease states suggest that the alleles of the MYH15 gene are differentially regulated by hypoxia.

Neary (2014) attempted to identify chromosomal regions associated with PAP and traits associated with mean PAP in calves. Using a high-density genome-wide association study, seven single nucleotide polymorphisms (**SNP**) were associated with mean PAP in animals at 4 months of age. The SNP found were associated with cellular proliferation, and susceptibility to myocardial and infectious disease. Two SNP were found to be associated with systolic PAP at 6 months of age, one of which was found in a region that could be indicative of the role hemostasis plays in determining susceptibility to PH.

Another study by Newman et al. (2015) evaluated the Endothelial PAS domain-containing protein 1 (**EPAS1**) gene. Angus bulls (n = 41) from 3 different ranches were sampled, with 21 of the animals sampled considered to have normal PAP measurements and the remaining 20 considered hypertensive. It was determined that the EPAS1 gene has two variants located in exon 12 that were associated with high altitude PH. These two variants are not reported in similar, high altitude tolerant species such as the yak and sheep. In contrast, preliminary results from Crawford et al. (2016) evaluating 47 Angus bulls and heifers, indicated that the EPAS1 gene may not be effective in distinguishing high PAP from low PAP animals. These results indicated that genotype of the EPAS1 gene was not a significant predictor of mean

PAP. Differences in these studies could be due to small sample sizes, as well as differences in sample populations.

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.

Alexander, A. F., and R. Jensen. 1963. Pulmonary vascular pathology of bovine high mountain disease. Am. J. Vet. Med. 24:1098-1111.

Angel, K. L. and J. W. Tyler. 1992. Pulmonary hypertension and cardiac insufficiency in three cows with primary lung disease. J. Vet. Int. Med. 6:214-219.

Chin, K. M., & Rubin, L. J. (2008). Pulmonary arterial hypertension. Journal of the American College of Cardiology, 51(16), 1527-1538.

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., X. Zeng, S. J. Coleman, T. N. Holt, S. E. Speidel, R. M. Enns, J. H. Newman, R. Hamid, and M. G. Thomas. 2016. 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. 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.

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

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.

Glover, G. H., and I. E. Newsom. 1915. Brisket Disease: Bulletin. No. 204. Colorado Agricultural College, Fort Collins, Colorado.

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

Hecht, H. H., H. Kuida, R. L. Lange, J. L. Thorne, and A. M. Brown. 1962. Brisket disease: II. Clinical features and hemodynamic observations in altitude-dependent right heart failure of cattle. Am. J. Med. 32:171-183.

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.

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.

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

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.

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., 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.

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.

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.

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.

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., J. L. Hicks, C. S. Card, and A. F. Alexander. 1975. Inherited susceptibility of cattle to high-altitude pulmonary hypertension. J. App. Phys. 38:491-494.

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.

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.

CHAPTER 3

EVALUATION OF ELEVATION EFFECTS ON PULMONARY ARTERIAL PRESSURE MEASURES IN ANGUS CATTLE

SUMMARY

Pulmonary hypertension (PH) due to hypoxia in cattle has typically been a disease associated with exposure to high altitude. Initially the disease was thought to only occur at extreme high elevations (> 2,400 m), but more recently it has been observed increasingly at elevations lower than 1500 m. Pulmonary arterial pressure (PAP) observations have been used as an indicator for an animal's susceptibility to PH with lower observations being favorable. However, these observations were only considered valid when they were recorded at elevations of 1,524 m and above. Yet, if observations from lower elevations were reliable, a greater number of records could be collected and used for selection and genetic improvement. Therefore; the objective of this study was two-fold:

1. To evaluate the relationship between PAP observations and elevation, as well as;
2. To determine if PAP observations obtained at low elevation have a strong genetic relationship with PAP observations obtained at high elevations.

We hypothesized that PAP observations obtained at low elevation are not perfectly related at the genetic level to PAP observations obtained at high elevations.

Data for this study (n = 14,665) were obtained from the American Angus Association (AAA), Colorado State University Beef Improvement Center (CSU-BIC), and Dr. Timothy Holt DVM (TH). A univariate model with a random, categorical elevation effect was utilized to

evaluate the relationship between PAP and elevation. Elevation solutions were obtained from the univariate analysis and paired with their corresponding elevation. Quadratic and cubic polynomial regressions were then compared to determine the best fit for the data, as well as to determine the elevation where PAP observations began to increase. The quadratic polynomial regression was established as the best fit for the data, and PAP observations began to increase above 1,620 m. A bivariate model was then used to evaluate the relationship between PAP observations obtained above and below 1,620 m. Resulting heritability estimates for high and low elevation PAP observations were 0.34 ± 0.03 and 0.29 ± 0.09 respectively. The estimated genetic correlation between these traits was 0.83 ± 0.15, suggesting that PAP observation are highly, but less than perfectly related when collected at high and low elevations.

INTRODUCTION

Pulmonary hypertension (**PH**), commonly known as brisket disease, is an illness that typically affects cattle located at high elevations. This condition develops due to a lack of atmospheric oxygen, which causes the cardiovascular system to compensate in order to supply sufficient levels of oxygen to the body (Holt and Callan, 2007). Additional load on the cardiovascular system for extended periods of time can cause PH, and in turn may eventually lead to right-side heart failure (**RHF**). The healthy bovine cardiopulmonary system does not utilize oxygen efficiently, so when the system becomes stressed it can fail quickly (Viet and Farrell, 1978).

Beef cattle producer reports initially indicated that brisket disease only occurred at elevations greater than 2,400 m (Glover and Newsom, 1915). Holt and Callan (2007) have since

reported incidences at elevations greater than 1,524 m, and this elevation has been commonly accepted as the threshold for what is considered high altitude for beef cattle producers in the western mountain region of the United States. This elevation is solely based off beef cattle producer reports, and no previous research has attempted to quantify the effect of elevation on cattle pulmonary arterial pressure (**PAP**) observations on the genetic level. Therefore, the first objective of this study was to evaluate the relationship between PAP observations and elevation.

Pulmonary arterial pressure observations are typically collected from cattle at high elevation to determine the presence or degree of PH. Most beef cattle producers at low elevations do not PAP test their cattle since they are not commonly affected by PH, and PAP observations collected at these elevations are not considered a reliable predictor of susceptibility to brisket disease (Holt and Callan, 2007). As a result, most high altitude producers will only introduce new genetics into their herd originating from other high altitude beef production systems. The relative value of PAP observations obtained from cattle located at lower elevations for selection purposes is currently unclear. Therefore, the second objective of this study sought to quantify the genetic relationship between high elevation PAP (**HPAP**) observations and low elevation PAP (**LPAP**) observations. An outcome of this assessment will be to determine level of sire re-ranking across elevations.

MATERIALS AND METHODS

Animal care and use committee approval was not obtained for this study because data was obtained from existing historical databases.

Data Description

Pulmonary arterial pressure observations, elevation, and management data were obtained from the American Angus Association (**AAA**; St. Joseph, MO), the Colorado State University Beef Improvement Center (**CSU-BIC**; Saratoga, WY), and from Dr. Tim Holt DVM (**TH**; Fort Collins, CO). All records used for these analyses were from Angus sired cattle born between 1985 and 2015. The initial data contained cattle that were PAP tested between 180 and 3,600 d of age, however, only cattle with PAP observations made between 270 and 720 d of age were used in this study, with a mean age at PAP collection of 402 ± 102 d. This age range was utilized as to include cattle that had a fully developed cardiopulmonary system, but not cattle that potentially could be experiencing age induced pulmonary arterial remodeling. A 3-generation pedigree was constructed from the final data file of animals (n = 14,665), resulting in a pedigree containing 25,226 animals, with 2,299 unique sires and 9,743 unique dams.

Contemporary group (**CG**) for PAP was defined as the combination of herd, PAP date, and yearling date. Contemporary groups containing offspring of a single sire, and those with no variance for PAP observations were removed from the analysis, resulting in 349 unique groups with an average of 42 individuals per group. Table 3.1 summarizes the performance records for PAP from each data source, and Figure 3.1 displays the distribution of PAP observations.

Table 3.1. Descriptive statistics of mean pulmonary arterial pressure observations by source.

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

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

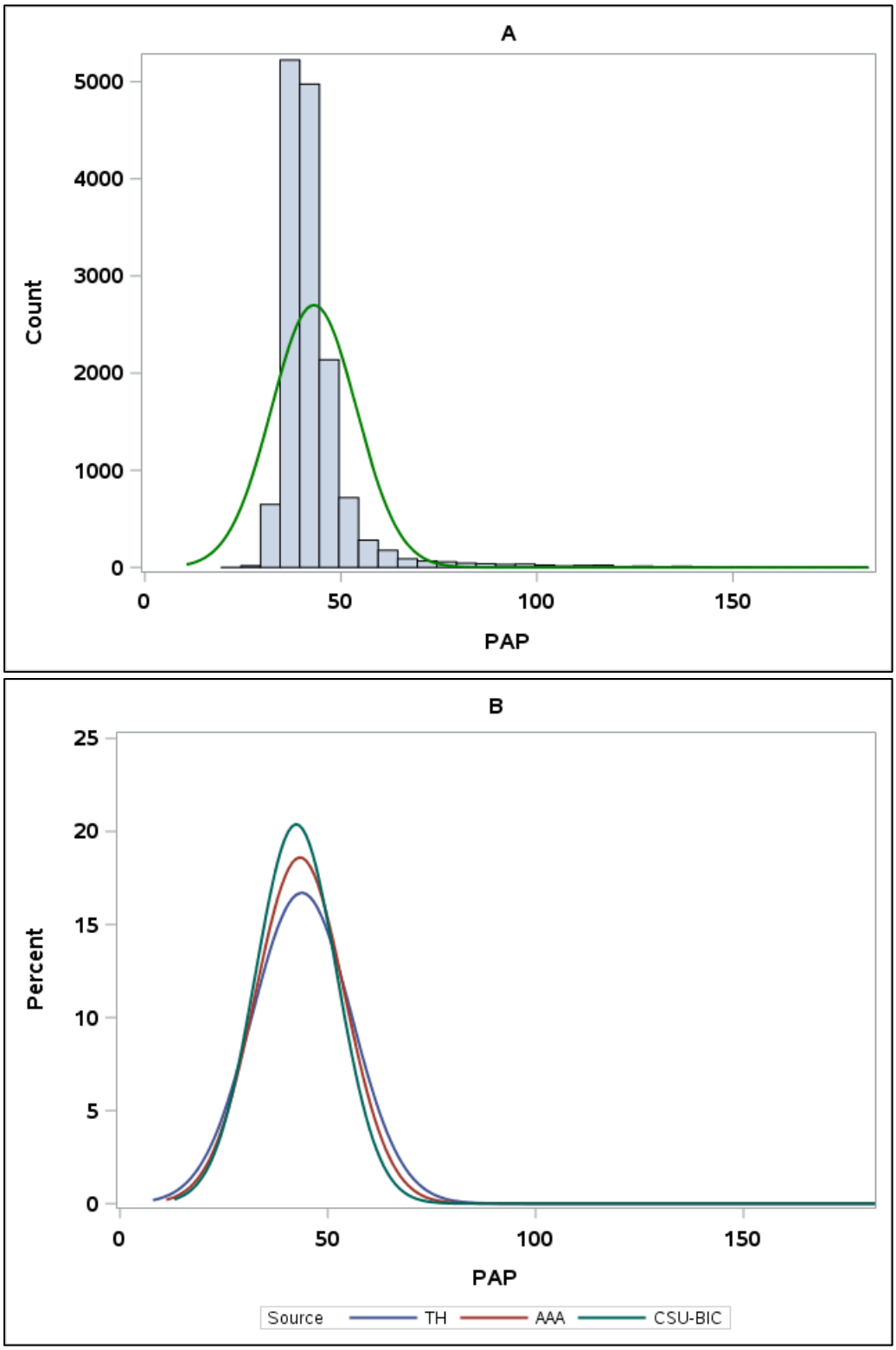

Figure 3.1 (A) Histogram and distribution of pulmonary arterial pressure (PAP) observations from American Angus Association (AAA), Colorado State University Beef Improvement Center (CSU-BIC), and Dr. Tim Holt DVM (TH), (B) Distribution curves of pulmonary arterial pressure (PAP) observations by source

Statistical Analysis

Univariate Analysis

Results from this study were obtained using the statistical software ASREML 3.0 (Gilmour et al., 2009). A univariate model was used to quantify the environmental relationship between PAP observations and elevation (objective 1). This was followed by a bivariate analysis evaluating the genetic relationship between PAP observations obtained at high and low elevations (objective 2).

A univariate animal model was utilized to identify the elevation where the distribution and mean of PAP observations began to increase. This univariate animal model was expressed as:

$$\boldsymbol{y} = \boldsymbol{Xb} + \boldsymbol{Zu} + \boldsymbol{e},$$

where $\boldsymbol{y}$ was a vector of PAP observations, $\boldsymbol{b}$ was a vector of fixed effect solutions, $\boldsymbol{u}$ was a vector of random effect solutions, and $\boldsymbol{e}$ was a vector of residual errors. $\boldsymbol{X}$ and $\boldsymbol{Z}$ represented incidence matrices relating fixed and random effects to the observations in $\boldsymbol{y}$.

The fixed effects included in the single trait analysis of PAP consisted of sex and age at PAP collection, which was modeled as a covariate. Wald F statistics were used to test the significance of fixed effects in the analysis, where all fixed effects included in the model were significant ($P < 0.05$). The random effects included in the single trait analysis of PAP included a random categorical elevation (**ELEV**) effect. There were 147 unique ELEV in this data, with a mean of 1,887 m and a minimum and maximum of 1,219 m and 2,896 m respectively.

Polynomial Regression

Elevation solutions were obtained from the results of the single trait analysis of PAP, and regressed on their corresponding elevation (m). A quadratic as well as a cubic polynomial regression (Proc Orthoreg, SAS Inst. Inc., Cary, NC) were utilized to determine when elevation solutions began to increase. Where the polynomial regressions were expressed as:

$$Quadratic: \ \boldsymbol{ELEV\ solution = ELEV^{2} + ELEV + INTERCEPT}$$

$$Cubic: \quad \boldsymbol{ELEV\ solution = ELEV^{3} + ELEV^{2} + ELEV + INTERCEPT}$$

A Type III *F* test was utilized to evaluate fixed effects in the quadratic and cubic polynomial regression models to determine which model was the best fit for the data. After the appropriate model was selected, the lowest point on the regression line was identified to classify high elevation PAP (**HPAP**) observations versus low elevation PAP (**LPAP**) observations.

Bivariate Analysis

Once the specific elevation demarcation for HPAP and LPAP observations was determined, a bivariate animal model was used to estimate the genetic relationship between HPAP and LPAP observations. Summary statistics of PAP observations made above and below elevation are summarized in Table 3.2. Figure 3.2 illustrates the distribution for HPAP and LPAP observations.

Table 3.2. Descriptive statistics of pulmonary arterial pressure at high elevations and low elevations from AAA [1], CSU-BIC [2], and TH [3] data.

Item	n	Minimum	Mean	Maximum	SD
HPAP [4]	13,088	22	43	180	10.87
LPAP [5]	1,577	32	43	144	10.52

[1] American Angus Association
[2] Colorado State University Beef Improvement Center
[3] Dr. Tim Holt DVM
[4] Pulmonary arterial pressure observations obtained ≥ 1,620 m
[5] Pulmonary arterial pressure observation obtained < 1,620 m

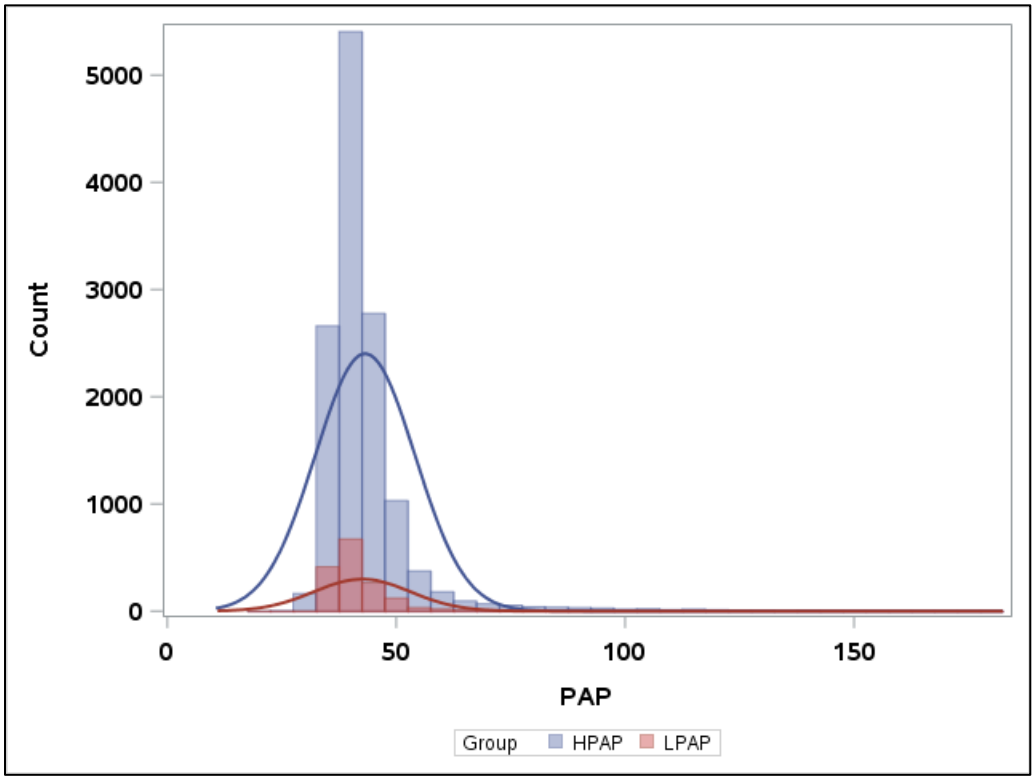

Figure 3.2. Histogram and density curve for high elevation pulmonary arterial pressure observations (HPAP) and low elevation pulmonary arterial pressure observations (LPAP)

The bi-variate analysis model in matrix form was expressed as:

$$\begin{bmatrix} \boldsymbol{y_1} \\ \boldsymbol{y_2} \end{bmatrix} = \begin{bmatrix} \boldsymbol{X_1} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{X_2} \end{bmatrix} \begin{bmatrix} \boldsymbol{b_1} \\ \boldsymbol{b_2} \end{bmatrix} + \begin{bmatrix} \boldsymbol{Z_1} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{Z_2} \end{bmatrix} \begin{bmatrix} \boldsymbol{u_1} \\ \boldsymbol{u_2} \end{bmatrix} + \begin{bmatrix} \boldsymbol{e_1} \\ \boldsymbol{e_2} \end{bmatrix}$$

where $\boldsymbol{y_i}$ was a vector of observations for the i^{th} trait, $\boldsymbol{b_i}$was a vector of unknown fixed effects for the i^{th} trait, $\boldsymbol{u_i}$ and $\boldsymbol{e_i}$ were vectors of random animal genetic and random residual effects for the i^{th} trait, respectively. $\boldsymbol{X_i}$ and $\boldsymbol{Z_i}$ were incidence matrices relating the observations in $\boldsymbol{y}$ to the fixed effects in $\boldsymbol{b}$ and random animal genetic effects in $\boldsymbol{u}$.

Fixed effects utilized in the bi-variate analysis were sex, age at PAP measurement, and CG. Additive direct genetic effects were included as a random effect. Wald F statistics were used to test significance of fixed effects in the analysis. All fixed effects included in the model were significant ($P < 0.05$).

The (co)variance of the random effects for the bivariate analysis was expressed as:

$$\boldsymbol{V} = \begin{bmatrix} \boldsymbol{d_1} \\ \boldsymbol{d_2} \\ \boldsymbol{e_1} \\ \boldsymbol{e_2} \end{bmatrix} = \begin{bmatrix} \boldsymbol{A\sigma^2_{d_1}} & \boldsymbol{A\sigma_{d_{12}}} & \boldsymbol{0} & \boldsymbol{0} \\ \boldsymbol{A\sigma_{d_{12}}} & \boldsymbol{A\sigma^2_{d_2}} & \boldsymbol{0} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{I\sigma^2_{e_1}} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{I\sigma^2_{e_2}} \end{bmatrix}$$

where $\boldsymbol{A}$ was Wright's numerator relationship matrix, $\boldsymbol{\sigma^2_{d_1}}$was the direct genetic variance for HPAP, $\boldsymbol{\sigma^2_{d_2}}$ was the direct genetic variance for LPAP, $\boldsymbol{\sigma_{d_{12}}}$ was the direct genetic covariance between HPAP and LPAP, $\boldsymbol{I}$was an identity matrix with an order equal to the number of observations in $\boldsymbol{y_i}$, $\boldsymbol{\sigma^2_{e_1}}$ was residual variance for HPAP, $\boldsymbol{\sigma^2_{e_2}}$ was residual variance for LPAP.

Spearman Rank Correlations

Sire estimated breeding values were obtained from the results of the bivariate analysis of HPAP and LPAP. Spearman rank correlations were used to rank sires with at least 10 progeny PAP tested across each elevation classification. Table 3.3 presents the number of sires by elevation, as well as average number of progeny per sire.

Table 3.3. Number of sires represented at high and low elevations, and average number of progeny per sire.

Elevation	n	Average Progeny
High [1]	635	21
Low [2]	112	14
Both	74	62

[1] ≥1,620 m
[2] < 1,620 m

RESULTS AND DISCUSSION

Univariate Analysis

The univariate analysis of PAP was utilized to obtain ELEV solutions to be input into a polynomial regression with the goal to identify the point at which PAP observations began to increase due to elevation. Elevation explained approximately 80 % of the variation in PAP observations. Since there was no random direct genetic effect utilized in the univariate analysis, no heritability estimate could be obtained.

Polynomial Regression

Quadratic Regression

Results obtained from the quadratic regression resulted in the equation:

$$\boldsymbol{y = 3.1852 * 10^{-6}x^2 - 0.0103x + 7.7778}$$

where **y** was the dependent variable ELEV solution from the univariate BLUP analysis, and **x** was the predictor variable ELEV (m). The *F* test for the quadratic regression model was significant ($P < 0.0002$). Type III F tests for the effects $ELEV^2$ and ELEV were both significant ($P \leq 0.05$), while the intercept was not ($P < 0.1388$). Figure 3.3 displays the scatter plot of ELEV solutions and their corresponding actual ELEV as well as the quadratic regression trend

line. The altitude corresponding to the lowest point on the regression trend line was found at approximately 1,620 m indicating that PAP observations began to increase above that elevation and a higher proportion of cattle located in this region would more likely be affected by PH. These results are in accordance with previous reports stating that hypoxia induced PH is typically only observed at elevations above 1,524 m (Holt and Callan, 2007).

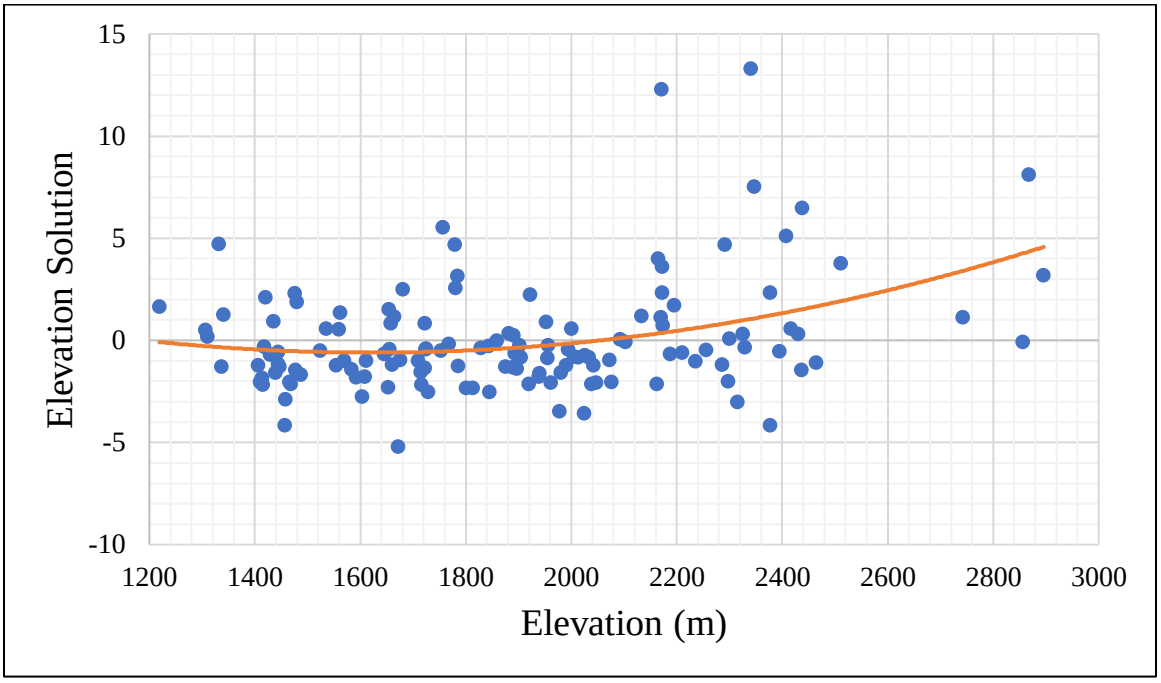

Figure 3.3. Elevation solutions by corresponding elevation plotted with a quadratic polynomial regression trend line

Cubic Regression

Results obtained from the cubic regression resulted in the equation:

$$y = -3.8596 * 10^{9}x^{3} + 2.6909 * 10^{-5}x^{2} - 0.0576x + 38.199$$

where the dependent and predictor variables were the same as in the quadratic regression. Figure 3.4 displays the scatter plot of ELEV solutions and their corresponding elevation as well as the

cubic regression trend line. The elevation corresponding to the lowest point on the regression trend line was approximately 1,670 m. This elevation agrees with previous reports stating that hypoxia induced PH is typically only observed at elevations above 1,524 m (Holt and Callan, 2007). The *F* test for the cubic regression model was significant ($P < 0.0003$), however the Type III *F* test for the fixed effects $ELEV^3$, $ELEV^2$, ELEV, and intercept were not significant ($P > 0.05$). Due to the fixed effects lack of significance in this model, we determined that the quadratic regression was the most appropriate analysis to define high versus low elevation (1,620 m).

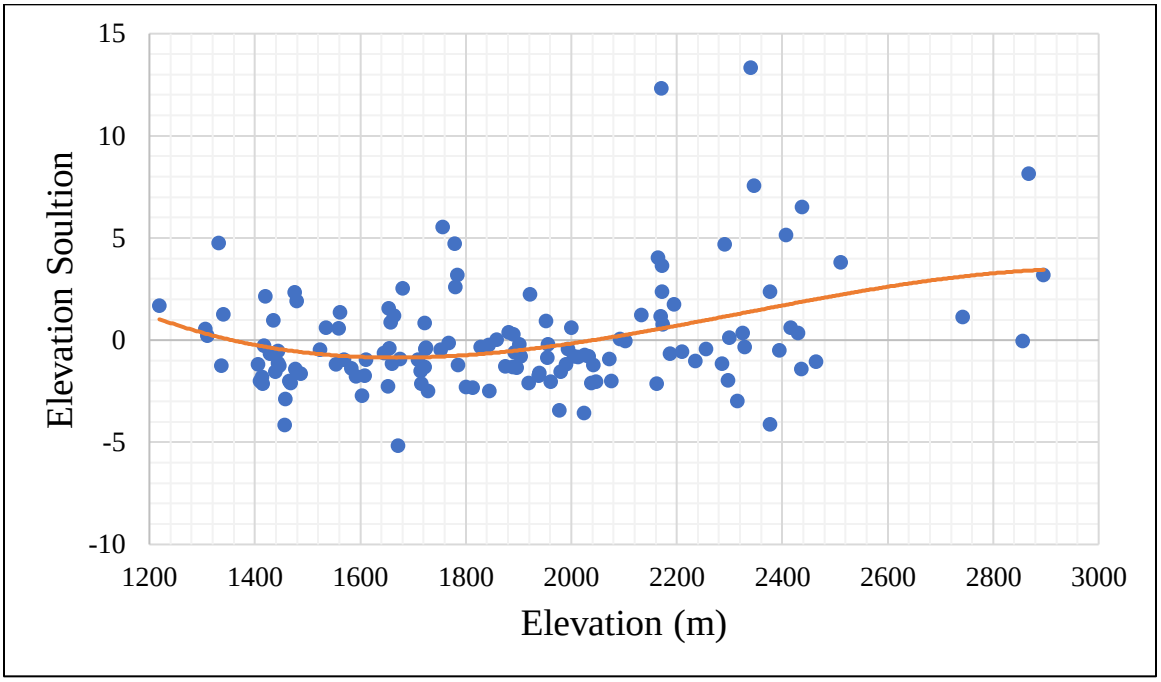

Figure 3.4. Elevation solutions by corresponding elevation plotted with a cubic polynomial regression trend line

Bi-variate Analysis

Results from the bi-variate analysis of HPAP and LPAP are displayed in Table 3.4. The heritability estimate for HPAP observations was 0.34 ± 0.03, while the heritability estimate for

LPAP observations was 0.29 ± 0.09. Both estimates were within the range of previously reported estimates in Hereford and Angus cattle (0.20 – 0.77; LeValley, 1978; Schimmel 1981; Enns et al., 1992; Cockrum et al., 2014 Zeng et al., 2014; Crawford et al., 2016). Similar research by Williams et al. (2012) evaluated the genetic relationship between growth traits (weaning weight and post-weaning gain) at differing altitudes. The authors utilized a correlation coefficient proposed by Robertson (1959) of 0.80, where a value less than that would be considered a biologically significant genotype by environment interaction. Based on a threshold of 0.80, the genetic correlation between HPAP and LPAP (0.83 ± 0.15) obtained in this study indicate that PAP observations can be considered the same trait regardless of elevation represented in this study.

Table 3.4. Heritabilities (diagonal; SE) and genetic correlation (above diagonal; SE) for pulmonary arterial pressure observations at high and low elevation from AAA[1], CSU-BIC [2], and TH [3] data

	HPAP [4]	LPAP [5]
HPAP [4]	0.34 (0.03)	0.83 (0.15)
LPAP [5]		0.29 (0.09)

[1] American Angus Association.
[2] Colorado State University Beef Improvement Center.
[3] Dr. Tim Holt DVM.
[4] Pulmonary arterial pressure observations obtained > 1,620 m.
[5] Pulmonary arterial pressure observation obtained ≤ 1,620 m.

It has typically been thought that PAP observations are only a reliable predictor of an animal's susceptibility to PH when obtained at high elevations. Due to the changes in atmospheric oxygen at varying elevations it is difficult to predict how an animal's individual PAP observation will change with elevation. However, results from the bivariate analysis

suggest that PAP observations obtained at low elevations (< 1,620 m) could be considered a reliable predictor of an animal's susceptibility to PH.

Spearman Rank Correlations

The Spearman rank correlation for sire estimated breeding values was 0.89. Due to the distribution of the data, there were only 27 sires with at least 10 progeny PAP tested at each elevation. Figure 3.5 Illustrates each of those 27 sire rankings by elevation.

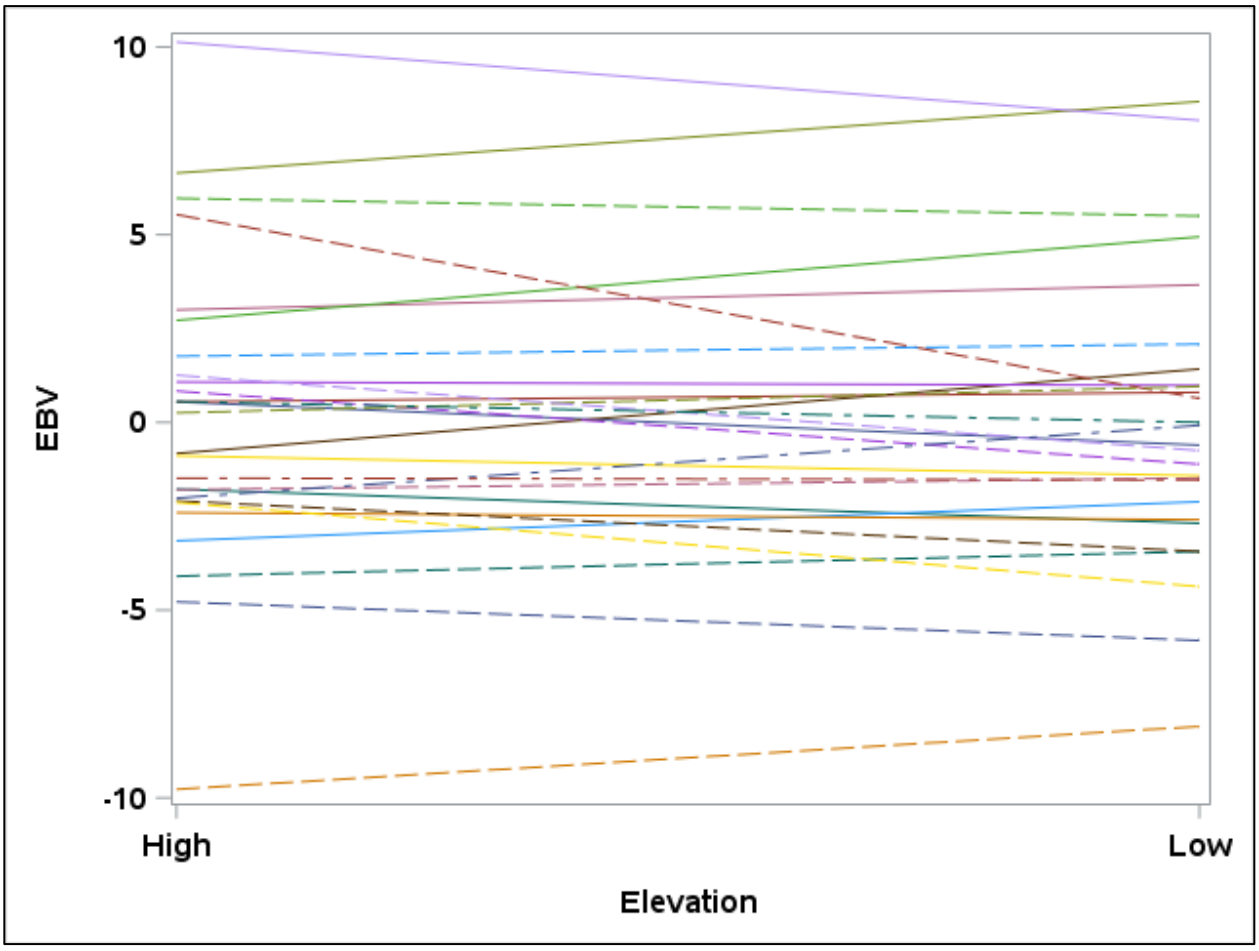

Figure 3.5 Sire estimated breeding value (EBV) by high (>1,620 m) and low (≤ 1,620 m) elevations, where each sire is represented by a different line

Results from the Spearman rank correlations of sire estimated breeding values suggested that there was some re-ranking of sire progeny performance across elevation albeit relatively small amounts.

Study Limitations

Since PH is a disease most commonly associated with high altitude, most producers located at low to moderate elevations do not PAP test their cattle, and this was evident in the data available for this research. The minimum elevation of PAP observations obtained for this study was approximately 1,200 m, which is still a greater elevation than most beef cattle production environments in the United States. Therefore, the relatively few number of LPAP observations (n = 1,577) in this study may not be an accurate representation of the population of cattle located below 1,620 m, and the genetic correlation estimate obtained from these results could change as information from even lower elevations is included.

CONCLUSIONS

Results from this study suggest that PAP may be considered a predictor of an animal's susceptibility to PH given the strong genetic relationships. These results also contradict previous comments by Holt and Callan (2007) which indicate that PAP observations are only reliable when they are made at elevations greater than 1,524 meters. If LPAP observations can be considered the same trait as HPAP observations, then high altitude beef producers could potentially utilize genetic resources from all elevations rather than just high elevation, provided PAP measures are available. Ultimately, for use in genetic improvement these two categories (high vs low) of PAP measures could be used in a multi-trait genetic evaluation to produce PAP

for high elevation outcomes. A clear limitation of the study results from the relatively few observations obtained below 1,620 m. There were also a limited number of sires that had offspring in both environments, so there were very limited genetic relationships between the high and low elevation populations. Due to the previously mentioned limitations these results may not be reliable below the elevations observed in this research.

LITERATURE CITED

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., 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.

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

Glover, G. H., and I. E. Newsom. 1915. Brisket Disease: Bulletin. No. 204. Colorado Agricultural College, Fort Collins, Colorado.

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

Robertson, A. 1959. The sampling variance of the genetic correlation coefficient. Biometrics 15:469-485.

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

Viet 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.

Williams, J. L., J. K. Bertrand, I. Misztal, and M. Lukaszewicz. 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.

CHAPTER 4

GENETIC PARAMETERS FOR PULMONARY ARTERIAL PRESSURE, PERFORMANCE TRAITS, AND CARCASS ULTRASOUND TRAITS IN ANGUS CATTLE

SUMMARY

Pulmonary arterial pressure (PAP) in cattle can be used as an indicator of susceptibility to develop right-sided heart failure (RHF) secondary to pulmonary hypertension in cattle. Heritability estimates of PAP have been previously determined to be moderate to high (0.20 to 0.77). Based on these estimates, selection for the indicator trait, PAP, could reduce the incidence of RHF due to hypoxia. Previous studies have speculated that increased growth rates and body fat accumulation contribute to increased PAP. Research evaluating the relationships between PAP and performance traits has yielded conflicting results regarding the genetic relationship between PAP, birth weight, and weaning weight. These conflicting results lead to ambiguity in the actual genetic relationship between PAP and performance traits. Additionally, no previous research has evaluated the relationship between PAP and carcass ultrasound traits. Therefore, the objective of this study was estimate heritability and genetic correlations between PAP observations, growth traits, and carcass ultrasound traits in Angus cattle, using data (n = 4,509) obtained from the American Angus Association. We hypothesized that traits associated with increased growth and muscle would have a positive genetic relationship with PAP. Estimates for heritability and genetic correlations were obtained using a multi-trait animal model. Heritability estimates for PAP (0.22 ± 0.04), BWT direct (0.35 ± 0.06), BWT maternal (0.15 ± 0.04), WW direct (0.20 ± 0.04), WW maternal (0.26 ± 0.05), PWG (0.28 ± 0.04) and YW

direct (0.36 ± 0.06) and YW maternal (0.13 ± 0.04) were within the range of estimates previously reported. Results revealed moderate genetic correlations between PAP and birth weight (BWT) maternal at 0.55 ± 0.14. Genetic correlations were weak (< 0.20) between PAP and BWT direct, direct and maternal weaning weight (WW), post-weaning gain (PWG), as well as direct and maternal yearling weight (YW). A moderate genetic correlation between PAP and ultrasound ribeye area (REA) was found at (0.24 ± 0.12). Genetic correlations between PAP, ultrasound back fat (BF), ultrasound intramuscular fat (IMF), and ultrasound rump fat (RUMP) were weak (ranging from -0.03 to 0.10) with heritability estimates for BF (0.43 ± 0.05), REA (0.30 ± 0.04), IMF (0.35 ± 0.04), and RUMP (0.47 ± 0.05) within the range of estimates previously reported. These results suggest that selection for increased birth weight and muscle mass (i.e. ribeye area) may consequently increase PAP observations while selection for other traits would likely cause little change in PAP.

INTRODUCTION

Historically, right-sided heart failure (**RHF**) due to pulmonary hypertension (**PH**) only affected cattle raised at high elevations. However, recent research has indicated that RHF secondary to PH is becoming increasingly problematic in feedlot cattle not located at high elevations (Jensen et al.,1976; Neary et al., 2015; 2016). These researchers speculated that respiratory disease, body fat accumulation, and high growth rates could be contributing to the increased incidence of RHF in feedlot cattle.

Pulmonary arterial pressure (**PAP**) measures are used to determine the presence and magnitude of PH in cattle. Moderate to high heritability estimates (0.20 – 0.77; Cockrum et al.,

2014; Schimmel, 1982) of PAP indicate that selecting for lowered PAP observations should result in lowered PAP observations in future generations. However, after generations of selection for decreased PAP observations, beef cattle producers still report incidences of calf death loss due to RHF. Many cattle producers also select for increased performance traits (growth and carcass quality). Previous research has speculated that selection for improved growth and carcass quality may increase metabolic oxygen demands and thereby increase PAP (Neary et al., 2016; Jensen et al, 1976).

There has been limited research evaluating the genetic relationships between growth traits and PAP. Shirley et al. (2008) reported moderate genetic correlations between PAP and birth weight (**BWT**) direct and weaning weight (**WW**) direct at 0.49 ± 0.12 and 0.51 ± 0.18, respectively in Angus cattle. Similarly, Crawford, et al. (2016) reported a moderate genetic correlation between PAP and WW direct of 0.22 ± 0.08, also in Angus cattle. These studies suggested that selection for increased growth rates may result in increased PAP observations. No previous research has evaluated the genetic relationships between PAP and carcass ultrasound traits. Increased growth and carcass quality have been major selection criteria in Angus cattle for the last 3 to 4 decades (http://www.angus.org/Nce/GeneticTrends.aspx), therefore, estimating their genetic relationships with PAP are warranted.

The objective of this research was to determine the genetic relationships between PAP and performance traits including BWT, WW, yearling weight (**YW**), post-weaning gain (**PWG**), ultrasound back fat (**BF**), ultrasound ribeye area (**REA**), ultrasound intramuscular fat (**IMF**), and ultrasound rump fat (**RUMP**). Our hypothesis was that traits associated with increased growth and muscle mass would have a positive genetic correlation with increased PAP observations.

MATERIALS AND METHODS

Animal Care and Use Committee approval was not obtained for this study because data were obtained from an existing historical database.

Data Description

Growth, carcass ultrasound, and PAP records were obtained from the American Angus Association (**AAA**; St. Joseph, MO). Records were from registered Angus cattle born between 1985 and 2015. The initial data contained cattle that were PAP tested between 188 and 3,482 d of age; however, only cattle with PAP observations made between 270 and 720 d were used in this study. This age range was utilized as to include cattle that had a fully developed cardiopulmonary system, but not cattle that potentially could be experiencing age induced pulmonary arterial remodeling. After data editing and sifting, the mean age of animals at PAP measurement was 452 ± 85 d. A 3-generation pedigree was constructed from the final data file (n=4,509), resulting in a pedigree containing 15,296 animals, with 2,025 unique sires and 8,327 unique dams.

Contemporary group (**CG**) for PAP were defined as a combination of herd, PAP date, and yearling date resulting in 109 unique groups with an average of 41 ± 63 individuals. Birth CG was defined as animals in the same birth year, weaning herd, and weaning management group. Weaning CG was defined as weaning herd, weaning date, and weaning management. Yearling CG was defined as yearling herd, yearling date, and yearling management group. Carcass ultrasound CG was defined as yearling CG and ultrasound date. Contemporary groups containing offspring of a single sire or CG's with no phenotypic variance were excluded from the analyses. Age of dam of animals was classified based on Beef Improvement Federation

guidelines (2010). Phenotypic observations on all performance traits (excluding PAP) that were beyond 5 SD from the overall mean were excluded from the analysis. Performance and PAP records used for these analyses are summarized in Table 4.1.

Table 4.1. Descriptive statistics of mean pulmonary arterial pressure, birth weight, weaning weight, yearling weight, post-weaning gain, ultrasound back fat, ultrasound ribeye area, ultrasound intramuscular fat, ultrasound rump fat from American Angus Association data

Item [1]	n	Minimum	Mean	Maximum	SD
PAP, mm Hg	4,509	30	43	180	10.72
BWT, kg	4,449	22	37	54	4.19
WW, kg	4,491	158	270	435	36.70
YW, kg	4,509	222	447	658	68.19
PWG, kg	4,491	3	167	344	60.04
BF, mm	3,688	1.02	4.83	15.24	2.29
REA, cm [2]	3,685	28.94	72.42	109.41	11.57
IMF, %	3,685	1.05	3.37	7.96	0.92
RUMP, mm	3,690	1.02	5.33	17.02	2.54

[1] PAP = mean pulmonary arterial pressure; BWT = birth weight; WW = weaning weight; YW = yearling weight; PWG = post-weaning gain; BF = ultrasound back fat; REA = ultrasound ribeye area; IMF = ultrasound intramuscular fat; RUMP = ultrasound rump fat.

Statistical Analysis

Results for this study were obtained using the statistical program ASREML 3.0 (Gilmour et al., 2009). Two 4-trait analyses were conducted to obtain heritability and genetic correlation estimates between PAP and growth traits. The first 4-trait analysis included PAP, BWT, WW, and YW. The second 4-trait analysis included PAP, BWT, WW, and PWG. For this analysis PWG was calculated as:

$$\mathbf{PWG = [(}YW - WW\mathbf{)/}\boldsymbol{days\ between\ weights}\mathbf{]} * \mathbf{160.}$$

Due to the high genetic correlation between PWG and YW as a result of the part-whole relationship, two analyses were performed where these traits were modeled separately with the other performance traits.

The 4-trait animal model including PAP, BWT, WW, and YW was expressed as follows,

$$\begin{bmatrix} \boldsymbol{y_1} \\ \boldsymbol{y_2} \\ \boldsymbol{y_3} \\ \boldsymbol{y_4} \end{bmatrix} = \begin{bmatrix} \boldsymbol{X_1} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{X_2} & \boldsymbol{0} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{X_3} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{X_4} \end{bmatrix} \begin{bmatrix} \boldsymbol{b_1} \\ \boldsymbol{b_2} \\ \boldsymbol{b_3} \\ \boldsymbol{b_4} \end{bmatrix} + \begin{bmatrix} \boldsymbol{Z_{a_1}} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{Z_{a_2}} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{Z_{m_2}} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{Z_{a_3}} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{Z_{m_3}} & \boldsymbol{0} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{Z_{a_4}} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{Z_{m_4}} \end{bmatrix} \begin{bmatrix} \boldsymbol{u_{a_1}} \\ \boldsymbol{u_{a_2}} \\ \boldsymbol{u_{m_2}} \\ \boldsymbol{u_{a_3}} \\ \boldsymbol{u_{m_3}} \\ \boldsymbol{u_{a_4}} \\ \boldsymbol{u_{m_4}} \end{bmatrix} + \begin{bmatrix} \boldsymbol{e_1} \\ \boldsymbol{e_2} \\ \boldsymbol{e_3} \\ \boldsymbol{e_4} \end{bmatrix},$$

with the genetic (co)variances equal to:

$$\boldsymbol{var} \begin{bmatrix} \boldsymbol{u_{a_1}} \\ \boldsymbol{u_{a_2}} \\ \boldsymbol{u_{m_2}} \\ \boldsymbol{u_{a_3}} \\ \boldsymbol{u_{m_3}} \\ \boldsymbol{u_{a_4}} \\ \boldsymbol{u_{m_4}} \end{bmatrix} = \begin{bmatrix} \boldsymbol{\sigma^2_{a_1}} & \boldsymbol{\sigma_{a_{12}}} & \boldsymbol{\sigma_{a_1 m_2}} & \boldsymbol{\sigma_{a_{13}}} & \boldsymbol{\sigma_{a_1 m_3}} & \boldsymbol{\sigma_{a_{14}}} & \boldsymbol{\sigma_{a_1 m_4}} \\ \boldsymbol{\sigma_{a_{12}}} & \boldsymbol{\sigma^2_{a_2}} & \boldsymbol{\sigma_{a_2 m_2}} & \boldsymbol{\sigma_{a_{23}}} & \boldsymbol{\sigma_{a_2 m_3}} & \boldsymbol{\sigma_{a_{24}}} & \boldsymbol{\sigma_{a_2 m_4}} \\ \boldsymbol{\sigma_{a_1 m_2}} & \boldsymbol{\sigma_{a_2 m_2}} & \boldsymbol{\sigma^2_{m_2}} & \boldsymbol{\sigma_{a_3 m_2}} & \boldsymbol{\sigma_{m_2 m_3}} & \boldsymbol{\sigma_{a_4 m_2}} & \boldsymbol{\sigma_{m_2 m_4}} \\ \boldsymbol{\sigma_{a_{13}}} & \boldsymbol{\sigma_{a_{23}}} & \boldsymbol{\sigma_{a_3 m_2}} & \boldsymbol{\sigma^2_{a_3}} & \boldsymbol{\sigma_{a_3 m_3}} & \boldsymbol{\sigma_{a_{34}}} & \boldsymbol{\sigma_{a_3 m_4}} \\ \boldsymbol{\sigma_{a_1 m_3}} & \boldsymbol{\sigma_{a_2 m_3}} & \boldsymbol{\sigma_{m_2 m_3}} & \boldsymbol{\sigma_{a_3 m_3}} & \boldsymbol{\sigma^2_{m_3}} & \boldsymbol{\sigma_{a_4 m_3}} & \boldsymbol{\sigma_{m_3 m_4}} \\ \boldsymbol{\sigma_{a_{14}}} & \boldsymbol{\sigma_{a_{24}}} & \boldsymbol{\sigma_{a_4 m_2}} & \boldsymbol{\sigma_{a_{34}}} & \boldsymbol{\sigma_{a_4 m_3}} & \boldsymbol{\sigma^2_{a_4}} & \boldsymbol{\sigma_{a_4 m_4}} \\ \boldsymbol{\sigma_{a_1 m_4}} & \boldsymbol{\sigma_{a_2 m_4}} & \boldsymbol{\sigma_{m_2 m_4}} & \boldsymbol{\sigma_{a_3 m_4}} & \boldsymbol{\sigma_{m_3 m_4}} & \boldsymbol{\sigma_{a_4 m_4}} & \boldsymbol{\sigma^2_{m_4}} \end{bmatrix} \otimes \boldsymbol{A}$$

and residual (co)variances equal to:

$$\boldsymbol{var} \begin{bmatrix} \boldsymbol{e_1} \\ \boldsymbol{e_2} \\ \boldsymbol{e_3} \\ \boldsymbol{e_4} \end{bmatrix} \begin{bmatrix} \boldsymbol{\sigma^2_{e_1}} & \boldsymbol{\sigma_{e_{12}}} & \boldsymbol{\sigma_{e_{13}}} & \boldsymbol{\sigma_{e_{14}}} \\ \boldsymbol{\sigma_{e_{12}}} & \boldsymbol{\sigma^2_{e_2}} & \boldsymbol{\sigma_{e_{23}}} & \boldsymbol{\sigma_{e_{24}}} \\ \boldsymbol{\sigma_{e_{13}}} & \boldsymbol{\sigma_{e_{23}}} & \boldsymbol{\sigma^2_{e_3}} & \boldsymbol{\sigma_{e_{34}}} \\ \boldsymbol{\sigma_{e_{14}}} & \boldsymbol{\sigma_{e_{24}}} & \boldsymbol{\sigma_{e_{34}}} & \boldsymbol{\sigma^2_{e_4}} \end{bmatrix} \otimes \boldsymbol{I}$$

The 4-trait animal model that included PWG in the place of YW, along with PAP, BW, and WW was expressed as follows:

$$\begin{bmatrix} \boldsymbol{y_1} \\ \boldsymbol{y_2} \\ \boldsymbol{y_3} \\ \boldsymbol{y_4} \end{bmatrix} = \begin{bmatrix} \boldsymbol{X_1} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{X_2} & \boldsymbol{0} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{X_3} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{X_4} \end{bmatrix} \begin{bmatrix} \boldsymbol{b_1} \\ \boldsymbol{b_2} \\ \boldsymbol{b_3} \\ \boldsymbol{b_4} \end{bmatrix} + \begin{bmatrix} \boldsymbol{Z_{a_1}} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{Z_{a_2}} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{Z_{m_2}} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{Z_{a_3}} & \boldsymbol{0} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{Z_{m_3}} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{Z_{a_4}} \end{bmatrix} \begin{bmatrix} \boldsymbol{u_{a_1}} \\ \boldsymbol{u_{a_2}} \\ \boldsymbol{u_{m_2}} \\ \boldsymbol{u_{a_3}} \\ \boldsymbol{u_{m_3}} \\ \boldsymbol{u_{a_4}} \end{bmatrix} + \begin{bmatrix} \boldsymbol{e_1} \\ \boldsymbol{e_2} \\ \boldsymbol{e_3} \\ \boldsymbol{e_4} \end{bmatrix},$$

with the genetic (co)variances equal to:

$$\boldsymbol{var} \begin{bmatrix} \boldsymbol{u_{a_1}} \\ \boldsymbol{u_{a_2}} \\ \boldsymbol{u_{m_2}} \\ \boldsymbol{u_{a_3}} \\ \boldsymbol{u_{m_3}} \\ \boldsymbol{u_{a_4}} \end{bmatrix} = \begin{bmatrix} \boldsymbol{A\sigma^2_{a_1}} & \boldsymbol{A\sigma_{a_{12}}} & \boldsymbol{A\sigma_{a_1m_2}} & \boldsymbol{A\sigma_{a_{13}}} & \boldsymbol{A\sigma_{a_1m_3}} & \boldsymbol{A\sigma_{a_{14}}} \\ \boldsymbol{A\sigma_{a_{12}}} & \boldsymbol{A\sigma^2_{a_2}} & \boldsymbol{A\sigma_{a_2m_2}} & \boldsymbol{A\sigma_{a_{23}}} & \boldsymbol{A\sigma_{a_2m_3}} & \boldsymbol{A\sigma_{a_{24}}} \\ \boldsymbol{A\sigma_{a_1m_2}} & \boldsymbol{A\sigma_{a_2m_2}} & \boldsymbol{A\sigma^2_{m_2}} & \boldsymbol{A\sigma_{a_3m_2}} & \boldsymbol{A\sigma_{m_2m_3}} & \boldsymbol{A\sigma_{a_4m_2}} \\ \boldsymbol{A\sigma_{a_{13}}} & \boldsymbol{A\sigma_{a_{23}}} & \boldsymbol{A\sigma_{a_3m_2}} & \boldsymbol{A\sigma^2_{a_3}} & \boldsymbol{A\sigma_{a_3m_3}} & \boldsymbol{A\sigma_{a_{34}}} \\ \boldsymbol{A\sigma_{a_1m_3}} & \boldsymbol{A\sigma_{a_2m_3}} & \boldsymbol{A\sigma_{m_2m_3}} & \boldsymbol{A\sigma_{a_1m_2}} & \boldsymbol{A\sigma^2_{m_3}} & \boldsymbol{A\sigma_{a_2m_2}} \\ \boldsymbol{A\sigma_{a_{14}}} & \boldsymbol{A\sigma_{a_{24}}} & \boldsymbol{A\sigma_{a_4m_2}} & \boldsymbol{A\sigma_{a_{34}}} & \boldsymbol{A\sigma_{a_2m_2}} & \boldsymbol{A\sigma^2_{a_4}} \end{bmatrix} \otimes \boldsymbol{A}$$

and residual (co)variances equal to:

$$\boldsymbol{var} \begin{bmatrix} \boldsymbol{e_1} \\ \boldsymbol{e_2} \\ \boldsymbol{e_3} \\ \boldsymbol{e_4} \end{bmatrix} = \begin{bmatrix} \boldsymbol{\sigma^2_{e_1}} & \boldsymbol{\sigma_{e_{12}}} & \boldsymbol{\sigma_{e_{13}}} & \boldsymbol{\sigma_{e_{14}}} \\ \boldsymbol{\sigma_{e_{12}}} & \boldsymbol{\sigma^2_{e_2}} & \boldsymbol{\sigma_{e_{23}}} & \boldsymbol{\sigma_{e_{24}}} \\ \boldsymbol{\sigma_{e_{13}}} & \boldsymbol{\sigma_{e_{23}}} & \boldsymbol{\sigma^2_{e_3}} & \boldsymbol{\sigma_{e_{34}}} \\ \boldsymbol{\sigma_{e_{14}}} & \boldsymbol{\sigma_{e_{24}}} & \boldsymbol{\sigma_{e_{34}}} & \boldsymbol{\sigma^2_{e_4}} \end{bmatrix} \otimes \boldsymbol{I}$$

Genetic correlation and heritability estimates for PAP and carcass ultrasound traits were obtained using a 5-trait model, which included PAP, BF, REA, IMF and RUMP. The 5-trait animal model evaluating PAP and carcass ultrasound traits was expressed as follows:

$$\begin{bmatrix} \boldsymbol{y_1} \\ \boldsymbol{y_2} \\ \boldsymbol{y_3} \\ \boldsymbol{y_4} \\ \boldsymbol{y_5} \end{bmatrix} = \begin{bmatrix} \boldsymbol{X_1} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{X_2} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{X_3} & \boldsymbol{0} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{X_4} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{X_5} \end{bmatrix} \begin{bmatrix} \boldsymbol{b_1} \\ \boldsymbol{b_2} \\ \boldsymbol{b_3} \\ \boldsymbol{b_4} \\ \boldsymbol{b_5} \end{bmatrix} + \begin{bmatrix} \boldsymbol{Z_1} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{Z_2} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{Z_3} & \boldsymbol{0} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{Z_4} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{Z_5} \end{bmatrix} \begin{bmatrix} \boldsymbol{u_{a_1}} \\ \boldsymbol{u_{a_2}} \\ \boldsymbol{u_{a_3}} \\ \boldsymbol{u_{a_4}} \\ \boldsymbol{u_{a_5}} \end{bmatrix} + \begin{bmatrix} \boldsymbol{e_1} \\ \boldsymbol{e_2} \\ \boldsymbol{e_3} \\ \boldsymbol{e_4} \\ \boldsymbol{e_5} \end{bmatrix}$$

with the genetic (co)variance equal to:

$$\boldsymbol{var} \begin{bmatrix} \boldsymbol{u_{a_1}} \\ \boldsymbol{u_{a_2}} \\ \boldsymbol{u_{a_3}} \\ \boldsymbol{u_{a_4}} \\ \boldsymbol{u_{a_5}} \end{bmatrix} = \begin{bmatrix} \boldsymbol{\sigma^2_{a_1}} & \boldsymbol{\sigma_{a_{12}}} & \boldsymbol{\sigma_{a_{13}}} & \boldsymbol{\sigma_{a_{14}}} & \boldsymbol{\sigma_{a_{15}}} \\ \boldsymbol{\sigma_{a_{12}}} & \boldsymbol{\sigma^2_{a_2}} & \boldsymbol{\sigma_{a_{23}}} & \boldsymbol{\sigma_{a_{24}}} & \boldsymbol{\sigma_{a_{25}}} \\ \boldsymbol{\sigma_{a_{13}}} & \boldsymbol{\sigma_{a_{23}}} & \boldsymbol{\sigma^2_{a_3}} & \boldsymbol{\sigma_{a_{34}}} & \boldsymbol{\sigma_{a_{35}}} \\ \boldsymbol{\sigma_{a_{14}}} & \boldsymbol{\sigma_{a_{24}}} & \boldsymbol{\sigma_{a_{34}}} & \boldsymbol{\sigma^2_{a_4}} & \boldsymbol{\sigma_{a_{45}}} \\ \boldsymbol{\sigma_{a_{15}}} & \boldsymbol{\sigma_{a_{25}}} & \boldsymbol{\sigma_{a_{35}}} & \boldsymbol{\sigma_{a_{45}}} & \boldsymbol{\sigma^2_{a_5}} \end{bmatrix} \otimes \boldsymbol{A}$$

and the residual (co)variance equal to:

$$\boldsymbol{var} \begin{bmatrix} \boldsymbol{e_1} \\ \boldsymbol{e_2} \\ \boldsymbol{e_3} \\ \boldsymbol{e_4} \\ \boldsymbol{e_5} \end{bmatrix} = \begin{bmatrix} \boldsymbol{\sigma^2_{e_1}} & \boldsymbol{\sigma_{e_{12}}} & \boldsymbol{\sigma_{e_{13}}} & \boldsymbol{\sigma_{e_{14}}} & \boldsymbol{\sigma_{e_{15}}} \\ \boldsymbol{\sigma_{e_{12}}} & \boldsymbol{\sigma^2_{e_2}} & \boldsymbol{\sigma_{e_{23}}} & \boldsymbol{\sigma_{e_{24}}} & \boldsymbol{\sigma_{e_{25}}} \\ \boldsymbol{\sigma_{e_{13}}} & \boldsymbol{\sigma_{e_{23}}} & \boldsymbol{\sigma^2_{e_3}} & \boldsymbol{\sigma_{e_{34}}} & \boldsymbol{\sigma_{e_{35}}} \\ \boldsymbol{\sigma_{e_{14}}} & \boldsymbol{\sigma_{e_{24}}} & \boldsymbol{\sigma_{e_{34}}} & \boldsymbol{\sigma^2_{e_4}} & \boldsymbol{\sigma_{e_{45}}} \\ \boldsymbol{\sigma_{e_{15}}} & \boldsymbol{\sigma_{e_{25}}} & \boldsymbol{\sigma_{e_{35}}} & \boldsymbol{\sigma_{e_{45}}} & \boldsymbol{\sigma^2_{e_5}} \end{bmatrix} \otimes \boldsymbol{I}\ ,$$

where in all three, multi-trait models; $\boldsymbol{y_i}$was a vector of observations for trait *i,* $\boldsymbol{X_i}$ was an incidence matrix relating fixed effects to observations in $\boldsymbol{y_i}$, $\mathbf{b_i}$ was a vector of fixed effect solutions, $\boldsymbol{Z_{a_i}}$ was an incidence matrix relating additive (*a*) random effects to observations in $\boldsymbol{y_i}$, $\boldsymbol{u_{a_i}}$was a vector of random, direct additive genetic effect solutions, $\boldsymbol{Z_{m_i}}$ was an incidence matrix relating maternal (*m*) random additive genetic effects to observations in $\boldsymbol{y_i}$, $\mathbf{u_{mi}}$ was a vector of maternal additive genetic random effect solutions, and $\boldsymbol{e_i}$ was a vector of random residual errors for each record. The $\boldsymbol{A}$ was Wright's numerator relationship matrix, $\boldsymbol{\sigma^2_{a_i}}$ was the direct genetic

variance for trait *i*, $\boldsymbol{\sigma^2_{m_i}}$ was the maternal genetic variance for trait *i*, $\boldsymbol{\sigma_{a_{ij}}}$ was the direct genetic covariance between trait *i* and *j*, $\boldsymbol{\sigma_{a_i m_i}}$ was the covariance between the direct component of trait *i* and the maternal component of trait *i*, $\boldsymbol{\sigma^2_{e_i}}$ was the residual variance for trait *i*, and $\boldsymbol{\sigma_{e_{ij}}}$ was the residual covariance of traits *i* and *j*, $\otimes$ was the Kronecker product operator, $\boldsymbol{I}$ was an identity matrix with an order equal to the number of observations in $\boldsymbol{y_i}$.

Wald F statistics were used to test significance of the fixed effects used in each analysis. Fixed effects included in each analysis of the relationship between PAP and growth traits are shown in Table 4.2. Fixed effects included in the analysis of PAP and carcass ultrasound traits are included in Table 4.3. The fixed effect PAP CG was not a significant predictor ($P < 0.14$) for PAP in the multi-trait analysis of PAP, BWT, WW, and YW, however it was still included in the model to remain consistent with the other multi-trait analysis. All other fixed effects were significant ($P < 0.05$).

Table 4.2. Fixed and random effects included in the multi-trait animal model for mean pulmonary arterial pressure, birth weight, weaning weight, yearling weight, and post weaning gain from American Angus Association data.

	Model				
Effect[1]	PAP	BWT	WW	YW	PWG
Fixed					
Age	X		X	X	
Age of Dam		X	X	X	X
Sex	X				
PAPCG [2]	X				
BWCG [3]		X			
WWCG [4]			X		
YWCG [5]				X	X
Random					
Direct additive	X	X	X	X	X
Maternal additive		X	X	X	
Permanent environment		X	X	X	

[1] PAP = mean pulmonary arterial pressure; BWT = birth weight; WW = weaning weight; YW = yearling weight; PWG = post-weaning gain.
[2] Pulmonary arterial pressure contemporary group (CG) = PAP date, herd, and yearling date
[3] Birth weight contemporary group (CG) = Birth year, herd, weaning date, weaning group, and sex
[4] Weaning weight contemporary group (CG) = herd, weaning date, weaning group, and sex
[5] Yearling weight contemporary group (CG) = herd, yearling date, yearling group, and sex

Table 4.3. Fixed and random effects included in the multi-trait animal model for mean pulmonary arterial pressure, ultrasound back fat, ultrasound ribeye area, ultrasound intramuscular fat, and ultrasound rump fat from American Angus Association data

	Model				
Effect [1]	PAP	BF	REA	IMF	RUMP
Fixed					
Age	X	X	X	X	X
Sex	X	X	X	X	X
PAPCG [2]	X				
USNDCG [3]		X	X	X	X
Random					
Direct Additive	X	X	X	X	X

[1] PAP = mean pulmonary arterial pressure; BF = ultrasound back fat; REA = ultrasound ribeye area; IMF = ultrasound intramuscular fat; RUMP = ultrasound rump fat.
[2] Pulmonary arterial pressure contemporary group (CG) = PAP date, herd, and yearling date.
[3] Carcass ultrasound contemporary group (CG) = yearling weight contemporary group and ultrasound date.

RESULTS AND DISCUSSION

Multi-Trait Analyses of PAP and Growth Traits.

The two multi-trait analyses of PAP and growth traits provided heritability estimates for each trait was well as genetic correlations between the traits. Due to the collinearity of YW and PWG, separate models were used to evaluate the relationship between PAP and those growth traits, with the other traits remaining consistent across the 2 analyses. Results from the multi-trait analysis of PAP, direct and maternal BWT, WW, and YW are displayed in Table 4.4. A moderate genetic correlation between PAP and BWT maternal was found at 0.56 ± 0.14. Shirley et al. (2008) and Crawford et al. (2016) both reported a minimal genetic relationship between PAP and BWT maternal at 0.01 ± 0.17 and 0.14 ± 0.10 respectively. Taken together with the results from this research it appears likely that the relationship is positive.

A weak genetic correlation between PAP and WW direct was estimated at (0.15 ± 0.15), which is lower than previous estimates. Previous research by Shirley et al. (2008) and Crawford et al. (2016) reported moderate genetic correlations between PAP and WW direct at 0.51 ± 0.18 and 0.23 ± 0.09 respectively. Differences in estimates may be due to the age at PAP measurement, where estimates made by Shirley utilized PAP observations made at weaning, and estimates made by Crawford were obtained using yearling PAP observations which were closer to the average age of the observations used in this study. Average age at PAP measurement for this study was approximately 450 ± 85 d. In this analysis, the genetic correlation was found to be low (< 0.20) between PAP, BWT direct, WW maternal, and YW direct and maternal. The heritability estimate for PAP was 0.22 ± 0.04 which was within the range of previously reported

research evaluating Hereford and Angus cattle (LeValley, 1978; Zeng et al., 2014). Heritability estimates for all growth traits were found to be within the range of previously reported literature as well (Arnold et al., 1991; Gregory et al, 1995; Shirley et al. 2008; Crawford et al. 2016).

Table 4.4. Heritabilities (diagonal; SE) and genetic correlations (above diagonal; SE) from the 5-trait model for mean pulmonary arterial pressure, birth weight (direct and maternal), weaning weight (direct and maternal), and yearling weight (direct and maternal) from American Angus Association data

Trait [1]	PAP	BWT_d	BWT_m	WW_d	WW_m	YW_d	YW_m
PAP	0.22	-0.08	0.56	0.16	-0.15	0.02	-0.06
	(0.04)	(0.13)	(0.14)	(0.15)	(0.13)	(0.13)	(0.17)
BWT_d		0.35	-0.18	0.39	-0.09	0.34	-0.13
		(0.06)	(0.15)	(0.12)	(0.14)	(0.11)	(0.17)
BWT_m			0.15	0.17	0.10	0.01	0.12
			(0.04)	(0.18)	(0.15)	(0.16)	(0.18)
WW_d				0.20	-0.56	0.73	-0.61
				(0.04)	(0.12)	(0.08)	(0.15)
WW_m					0.26	-0.28	0.95
					(0.05)	(0.13)	(0.05)
YW_d						0.36	-0.48
						(0.06)	(0.12)
YW_m							0.13
							(0.04)

[1] PAP = mean pulmonary arterial pressure, BWT = birth weight, WW = weaning weight; YW = yearling weight. Subscript d indicates additive direct. Subscript m indicates additive maternal

Results from the multi-trait analysis of PAP, direct and maternal BWT, direct and maternal WW, and PWG are shown in Table 4.5. Heritability and genetic correlation estimates of PAP, BWT direct and maternal, and WW direct and maternal were similar to the estimates obtained from the multi-trait model that include YW. The heritability estimate for PWG (0.28 ± 0.04) was within the range of previously reported estimates in Angus, Hereford, and composite cattle (Schimmel, 1982; Bennett et al., 1996; Crawford et al., 2016). There was a minimal

genetic correlation between PAP and PWG (-0.06 ± 0.12). This supports previous findings by Crawford et al. (2016) which reported an estimate of -0.10 ± 0.10.

Table 4.5. Heritabilities (diagonal; SE) and genetic correlations (above diagonal; SE) from the 4-trait model for mean pulmonary arterial pressure, birth weight (direct and maternal), weaning weight (direct and maternal), and post-weaning gain from American Angus Association data

Trait [1]	PAP	BWT_d	BWT_m	WW_d	WW_m	PWG
PAP	0.22 (0.04)	-0.07 (0.13)	0.54 (0.14)	0.14 (0.15)	-0.15 (0.14)	-0.06 (0.12)
BWT_d		0.35 (0.06)	-0.18 (0.15)	0.45 (0.12)	-0.13 (0.15)	-0.14 (0.12)
BWT_m			0.15 (0.04)	0.16 (0.18)	0.11 (0.16)	-0.11 (0.14)
WW_d				0.20 (0.04)	-0.53 (0.13)	0.23 (0.14)
WW_m					0.20 (0.04)	-0.12 (0.13)
PWG						0.28 (0.04)

[1] PAP = mean pulmonary arterial pressure; BWT = birth weight; WW = weaning weight; PWG = post weaning gain. Subscript d indicates additive direct. Subscript m indicates additive maternal

Heritability estimates obtained from these analyses were lower than the heritability estimate (0.32 ± 0.03) obtained in Chapter 3. This is likely due to the difference in data utilized between the two studies, as the results from Chapter 3 were obtained using data from 3 sources, while this study only utilized data obtained from AAA. The moderate genetic correlation between PAP and BWT maternal is considerably larger than previous values reported by Shirley et al (2008) and Crawford et al. (2016) at 0.01 ± 0.17 and 0.14 ± 0.09 respectively. Estimates from these previous studies were obtained from two separate herds, both located at high elevation, while estimates from this research were obtained using data from approximately 120 different Angus seedstock herds located at various elevations (1,219 – 2,430 m). Both Angus herds evaluated by Shirley et al., (2008) and Crawford et al., (2016) placed heavy selection pressure on PAP observations. Differences in selection criteria and management of cattle could contribute to the dissimilar estimates between this research and previously reported research.

From a physiological standpoint, the relationship between PAP and the maternal influence on BWT has not been well documented in cattle. Maternal BWT is a function of blood flow to the fetus during gestation (Roland et al, 2012), and results from this study suggested that the more blood flow to the fetus, the more likely that calf is to have an elevated PAP observation. These results contradict previous physiological research in humans, which indicate that decreased birth weight may cause offspring blood pressure to increase (Law et al., 1996; Ho, 2014). Further research will need to be done to further examine the relationship between PAP and maternal BWT, but results from this study indicate that it is a positive relationship.

Multi-trait Analysis of PAP and Carcass Ultrasound Traits

Heritability and genetic correlation estimates for PAP and carcass ultrasound traits are displayed in Table 4.6. A moderate genetic correlation between PAP and REA was found at 0.24 ± 0.12. Genetic correlations between PAP, BF, IMF, and RUMP fat were low (< 0.20) and selection for these production traits would likely cause little change in PAP. The heritability estimate for PAP (0.21 ± 0.04) was found to be within the range (0.20 – 0.77) of previously reported literature (Enns et al.,1992; LeValley, 1978; Zeng et al., 2014). Similarly, heritability estimates for carcass ultrasound traits were all found to be within the range of previously reported literature in Angus, Hereford, and crossbred beef cattle (Arnold et al., 1991; Robinson et al., 1993; Reverter et al., 2000; Arthur et al., 2001; Su et al., 2016).

Table 4.6 Heritabilities (diagonal; SE) and genetic correlations (above diagonal; SE) from the 5-trait model for mean pulmonary arterial pressure, back fat, ribeye area, intramuscular fat, and rump fat from American Angus Association data

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

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

A previously suggested hypothesis is that increases in muscle mass and fat deposition may lead to increased PAP (Jensen et al., 1976; Neary et al., 2015), however the genetic relationship between these traits has not been previously evaluated. The moderate genetic correlation between PAP and REA (0.24 ± 0.12) reported in this study support that previous theory, that increased muscle mass is correlated with increased PAP. This also supports previous research by Lekeux et al. (1994) which suggested that Belgian Blue cattle, a "double-muscled" breed, were more susceptible to hypoxemia than other cattle breeds. Results from this study indicated that there is a minimal genetic relationship between PAP and fat deposition. However, in comparison, studies in humans have suggested that increases levels of obesity are associated with increased blood pressure, with a 10 kg increase in body weight corresponding to a 12 % increase in risk of heart disease (Hall, 2003; Poirier et al., 2006). Feedlot cattle are typically fed a high concentrate diet to promote increased growth rates and increased IMF, however this study only utilized data from bulls and heifers, likely to be used as replacement animals, and generally these cattle are managed in such a way to limit excessive fat deposition.

CONCLUSIONS

The results from the multi-trait analyses of PAP, growth traits and carcass ultrasound traits support our hypothesis that increased growth and muscle mass are genetically correlated to increased PAP observations in Angus cattle. Results suggested that there was a moderate genetic correlation between PAP and maternal BWT, as well as PAP and REA. There appeared to be no significant genetic correlation between PAP, BWT direct, WW direct and maternal, YW direct and maternal, ultrasound BF, ultrasound IMF, or ultrasound RUMP.

IMPLICATIONS

This information is important for beef producers to consider when making selection decisions, especially those located at high elevations, and. for consideration in directing the improvement of the Angus breed. Profitability in the beef industry is primarily driven by live animal weight or carcass quality. Continually selecting for improvement in these traits could inadvertently be increasing metabolic oxygen demands beyond the capability of the bovine cardiopulmonary system.

LITERATURE CITED

American Angus Association (AAA). 2016. Genetic trend EPD and $value by birth year. http://www.angus.org/Nce/GeneticTrends. aspx. (Accessed 4 December 2016).

Arnold, J. W., J. K. Bertrand, L. L. Benyshek, and C. Ludwig. 1991. Estimates of genetic parameters for live animal ultrasound, actual carcass data, and growth traits in beef cattle. J. Anim. Sci. 69:985-992.

Arthur, P. F., J. A. Archer, D. J. Johnston, R. M. Herd, E. C. Richardson, P. F. Parnell. 2001. Genetic and phenotypic variance and covariace components for feed intake feed efficiency, and other postweaning traits in Angus cattle. J. Anim. Sci. 79:2805-2811.

Beef Improvement Federation. 2010. Guidelines for uniform beef improvement programs, 9th ed. Beef Improv. Fed., Raleigh, NC. USA. p. 161.

Bennett, G. L., and K. E. Gregory. 1996. Genetic (co)variances among birth weight, 200-day weight, and postweaning gain in composites and parental breeds of beef cattle. J. Anim. Sci. 74:2598-2611.

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 analysis of pulmonary arterial pressure. In: Proc 10th World Cong. Genet. Appl. Livest. Prod., Vancouver, British Columbia, Canada.

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.

Gilmore, A. R., B. J. Gogel, B. R. Cullis, and R. Thompson. 2009. ASReml User Guide version 3.0. http://www.vsni.co.uk.

Gregory, K. E., L .V. Cundiff, and R. M. Koch. 1995. Genetic and phenotypic (co)variances for growth and carcass traits of purebred and composite populations of beef cattle. J. Anim. Sci. 73:1920-1926.

Hall, J. E. (2003). The kidney, hypertension, and obesity. Hypertension, 41(3), 625-633.

Ho. D. H. 2014. Transgenerational epigenetics: The role of maternal effects in cardiovascular development. Int. Comp. Bio. doi:10.1093/icb/icu031

Jensen, R., R. E. Pierson, P. M. Braddy, 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. Assoc. 169:515-517.

Law, C. M., and A. W. Shiell. 1996. Is blood pressure inversely related to birth weight? The strength of evidence from a systematic review of the literature. J. Hypertension. 14:935-942.

Lekeux, P., H. Amory, D. Desmecht, P. Gustin, A. Linden, and F. Rollin. 1994. Oxygen transport chain in double-muscled Blue Belgian cattle. British Vet. J., 150(5), 463-471.

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

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., 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.

Poirier, P., Giles, T. D., Bray, G. A., Hong, Y., Stern, J. S., Pi-Sunyer, F. X., & Eckel, R. H. (2006). Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss. Circulation, 113(6), 898-918.

Reverter, A., D. J. Johnston, H. U. Graser, M. L. Wolcott, and W. H. Upton. 2000. Genetic analyses of live-animal ultrasound and abattoir carcass traits in Australian Angus and Hereford cattle. J. Anim. Sci. 78:1786-1795.

Robinson, D. L., K. Hammond, and C. A. McDonald. 1993. Live animal measurement of carcass traits: estimation of genetic parameters for beef cattle. J. Anim. Sci. 71:1128 1135.

Roland, M. C. P., C. M. Friis, N. Voldner, K.Godang, J. Bollerslev, G. Haugen, and T. Henriksen. 2012. Fetal growth versus birthweight: the role of placenta versus other determinants. PLoS ONE 7(6): e39324. doi:10.1371/journal.pone.0039324.

Schimmel, J. G. and J. S. Brinks. 1982. The relationship of pulmonary arterial pressure with postweaning performance traits in yearling beef bulls. In. Proc. West. Sect. Am. Soc. Anim. Sci. 33:203-205.

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

Su. H., D. J. Garrick, B. Golden, and L. Hyde. 2016. Estimation of genetic parameters for carcass traits and their corresponding ultrasound measurements in crossbred beef cattle. Animal Industry Report: AS 662, ASL R3057.

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, and R. M. Enns. 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.