THESIS

PULMONARY ARTERIAL PRESSURE AS AN INDICATOR FOR HIGH ALTITUDE DISEASE IN CATTLE: BREED DIFFERENCES AND RELATIONSHIPS WITH GROWTH PERFORMANCE

Submitted by

Natalie Faye Crawford

Department of Animal Sciences

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Master's Committee:

Advisor: R. Mark Enns
Co-Advisor: Milton Thomas

Timothy Holt

ABSTRACT

PULMONARY ARTERIAL PRESSURE AS AN INDICATOR FOR HIGH ALTITUDE DISEASE IN CATTLE: BREED DIFFERENCES AND RELATIONSHIPS WITH GROWTH PERFORMANCE

High altitude disease (HAD), commonly known as brisket disease, is a natural occurring phenomenon in cattle. This disease occurs most often in high altitude (> 1,500 m) environments, where adaptability to the hypoxic conditions may be insufficient. Pulmonary arterial pressure (PAP) scores are the most useful tool available to cattle producers in predicting an animal's susceptibility to HAD. The all-encompassing objectives for this thesis were to delineate the important factors influencing PAP scores and understand the relationships between PAP scores and other performance traits, where selection for more favorable PAP may have adverse effects on those performance traits.

Two sources of data were used for this thesis: Historical records from the San Juan Basin Research Center, 4-Corners Bull Test (1983 to 2005; n = 2,041) and from the Colorado State University Beef Improvement Center (1993 to 2014; CSU-BIC; n = 8,718). For the 4-Corners study, data of yearling age and breed of cattle were used to determine how PAP varies with regards to both of these effects. The model of birth year, pen, breed, and yearling age effects on yearling PAP revealed these terms were all significant predictors of PAP ($P < 0.01$). With every one-day increase in yearling age, PAP increased by 0.03 (± 0.01) mm Hg ($P < 0.01$) with a mean PAP of 45.2 ± 12.8 mm Hg. Breed was found to be a highly significant factor ($P < 0.001$) in the model influencing PAP scores for bulls developed at high altitude. There was a 13.8-mm Hg

range between breeds with the lowest adjusted PAP estimate to those with the highest adjusted PAP. The results suggested that appropriate breed selection based on reduced PAP scores could be advantageous in reducing the susceptibility of cattle to HAD and subsequent death due to pulmonary hypertension and right heart failure.

The CSU-BIC data contained production weight traits of birth (36.2 ± 5.1), weaning (213.5 ± 31.8), yearling (345.6 ± 83.9), and post-weaning gain (121.9 ± 63.7) and PAP (42.4 ± 9.9) scores and these data were used to estimate heritabilities and relationships amongst them (mean ± SD; kg). Single-trait, two-trait, and multi-trait models revealed genetic correlations between PAP and the weight traits ranging from -0.11 ± 0.10 to 0.23 ± 0.08. An advantage to using a multi-trait model over a two-trait model is the increase in heritability due to the increase of information from more traits evaluated. Results of this study suggested that selection for lower PAP should not have adverse effects on the growth performance traits evaluated.

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CHAPTER 1

INTRODUCTION

The beef industry faces a multitude of concerns related to cattle management. These concerns include: illness and disease, predation, available resources, consumer preferences for taste and welfare, quality and food safety. Proper management of genetic and environmental influences that hinder the profitability of herds is the ultimate aim of all sectors of the beef industry. The genetic influences depend on parents, breed, the heritable nature of the trait, and genetically correlated traits. Some of the environmental factors affecting profitability include adaptability to elevation, season, temperature, maternal environment, and weed or vegetation exposure (Hohenboken et al., 2005). Changes in temperature, for instance due to seasonal changes, cold snaps in winter, movement of animals from a warm climate to cold climate, and failure of these animals to adapt to these changes can negatively affect production levels. Breeding and selection decisions potentially create productive and efficient animals that can adapt to these environmental changes, and reduce the potential detrimental effects these environmental factors have on production (Hohenboken et al., 2005).

Genetic progress of a particular trait through selection of animals based on phenotype can be accomplished by determining the heritable nature of the trait. Heritability is the proportion of phenotypic variation that is explained by additive genetic variation (Bourdon, 1999). Genetic gain through selection for a trait is dependent upon four factors: selection intensity, genetic variability, generation interval, and accuracy of selection. Increasing the intensity of selection, genetic variability, and accuracy of selection, along with decreasing the generation interval has the potential to increase the rate of genetic progress within a herd (Bourdon, 1999). Increasing

selection intensity in a herd can affect the profitability of the cow-calf sector by increasing rate of genetic gain through use of superior parents.

One issue affecting cow-calf and feedlot producers in high elevation regions (> 1,500 m) is the risk of developing high altitude disease (HAD), commonly known as brisket disease. This disease has been observed and studied since the early 20th century (Glover and Newsom, 1917), but no significant decrease in prevalence has been reported since that time (Malherbe et al., 2012; Neary et al., 2013). Pulmonary arterial pressure (PAP) test and its scores are the best-known indicator of an animal's susceptibility to HAD (Holt and Callan, 2007). The amount or degree increase in PAP scores is directly related to the degree of hypertrophy of the adventitia of small pulmonary arteries and ventricular workload leading to pulmonary hypertension and right-sided heart failure (Holt and Callan, 2007).

In order to decrease the incidence of HAD, it is pertinent to determine what genetic and environmental factors exist that effect the incidence of the disease. Previous research efforts pertaining to HAD and PAP include estimating the heritability, and genetic correlations of PAP between sexes, comparing healthy and 'brisket' animals, and regressing PAP on age of the animal (Will et al., 1975a; Schimmel and Brinks, 1983; Enns et al., 1992; Cockrum et al., 2014). Lacking in previous research is information on breed differences in PAP. Currently, PAP scores have not been compared between different breeds of *Bos indicus* or *Bos taurus* cattle. Determining if a difference in PAP exists between breeds would be useful to producers' breeding decisions at high altitude. Also lacking are the relationships between PAP and performance traits (e.g. BW, WW, etc.). Only two studies have examined PAP and weight trait genetic relationships. No knowledge of relationships among PAP and post-weaning gain has been researched. Gaining more understanding of these relationships will allow for better selection and

management for optimal performance and the potential of less cases of HAD due to decreased PAP scores. More knowledge could be achieved in determining the significant environmental factors affecting PAP scores and susceptibility of cattle to HAD. This will provide better selection and management procedures to producers at high altitudes looking to decrease the prevalence of HAD in their herds. Lastly, there is limited familiarity with what (if any) maternal influences there are on PAP scores. Due to the fact that relationships with weight and PAP are limited, the maternal influence on weight at different stages of an animal's life has the potential to alter PAP scores. This needs to be examined further.

This thesis enhances knowledge of the genetic and environmental influences on variability in PAP scores in beef cattle. The project objectives were to:

1. Examine breed differences in PAP.
2. Determine the associative relationship between growth performance and PAP.
3. Determine if maternal effects contribute significantly to variation in yearling PAP.

CHAPTER 2

REVIEW OF LITERATURE

In order for the beef industry to be profitable, cattle must be productive, efficient and produce a desirable end product (Hohenboken et al., 2005). To achieve balanced genetic potential for adaptation, production and product quality for herds within specific environments, selection programs must be implemented with this in mind. By doing so, the beef industry will have the opportunity to improve profitability of beef cattle production and to uphold the reliability of cattle production environments (Hohenboken et al., 2005). It is important for producers to realize what factors (i.e. environmental, genetic, maternal) influence cattle production, whether it is growth, reproduction, or quality of end products. Knowledge of such factors help to gauge in what areas we are able to make genetic progress through selection. As will be discussed in further detail in subsequent sections, high altitude disease (HAD) has hindered beef production systems at high elevations since the late 1800's. Cattle unable to cope with altitude can die from right heart failure, creating an economic hardship. Pulmonary arterial pressure (PAP) is an indicator trait of an animal's ability to cope with hypoxia of high altitude, and is currently used to make selection decisions in cattle ranches at high elevations. Therefore, it is important to examine and understand the factors (i.e. environment, genetics, maternal) that effect PAP scores and ultimately the susceptibility of an animal to HAD.

SECTION 1: ENVIRONMENTAL CHALLENGES AND THE GENETIC CONTRIBUTIONS TO ADAPTABILITY

The ability of cattle to adapt, and optimally perform, plays a key role in beef cattle production systems. Physical, chemical, biological, and environmental factors occur and effect the physiological reactions animals have to a particular environment (Johnson and Vanjonack, 1976). There is increasing importance in understanding environmental limitations for animals and in understanding what constitutes an optimal environment (Johnson and Vanjonack, 1976). Adaptability is key to sustaining livestock production systems, and potential benefits to improving adaptability include: enhanced animal well-being, enhanced resource conservation and forage utilization, increased profitability for beef cattle producers, and more desirable products for beef consumers (Hohenboken et al., 2005; Nardone et al., 2010).

1.1 GENERAL ENVIRONMENTAL CHALLENGES AFFECTING CATTLE

The keys to achieve genetic improvement for adaptation of beef cattle in America include: identifying important stressors and environmental challenges, quantifying genetic (co)variation of adaptive and production traits, and identifying indicator traits that are essential to adaptation (Hohenboken et al., 2005). Management practices such as use of implants and (or) ionophores, artificial insemination, rotational grazing systems, and good record keeping provide managers the opportunity to overcome some of the environmental obstacles or reduce the severity of their impact on these animals. The key environmental obstacles that hinder the ability of cattle to adapt to their surroundings include: micro-climate, season, weeds or vegetation exposure, management practices, and elevation and oxygen availability.

Climate and season play a vital part in determining the traits included in adaptability of cattle because of their effects on production levels, morbidly, and mortality. Acclimation can be defined as a phenotypic response developed by an animal to a single source of environmental stress (Fregly, 2011). Weather factors such as temperature, humidity, precipitation, wind, and atmospheric pressure can hinder the ability of cattle to adapt appropriately to a particular region. One challenge with beef cattle production systems as compared to the dairy, swine or poultry industry is the lack of control on environmental factors. Beef cattle are generally reared outdoors, exposed and especially vulnerable to extreme and rapid changing environmental conditions. When cattle try to acclimate and overcome the thermal challenges they face, they have reduced feed intake, alterations in productive and reproductive efficiency, and changes in physiological functions that are linked with health (Beede and Collier, 1986; Lacetera et al., 2006).

Ingestion of certain vegetation, for example tall fescue (*Festuca arundinacea*), a widely used cool-season grass, contributes to the adaptability of beef cattle to their environment (Pendlum et al., 1980). Fescue toxicosis is an animal condition associated with the consumption of a tall fescue cultivar infected with an endophyte, where poor animal gains, intolerance to heat, excessive salivation, rough hair coat, elevated body temperature, nervousness, lower milk production, and reduced feed consumption were observed (Stuedemann and Hoveland, 1988). Being able to effectively manage and select cattle for such an environment plays a key role in the susceptibility of an animal to disease. Selecting cattle for breeding stock that are best suited to a particular environment and tolerant of these environmentally triggered diseases would allow improvement in the genetics of those animals, and ultimately decrease susceptibility.

Another example includes facial eczema (FE) or *pithomycotoxicosis*. It is a disease found in ruminants (most notably in sheep or dairy cattle) that has an effect on the animal's liver (Di

Menna et al., 2009). Previous studies have found that indicators for an animal's susceptibility to this disease include elevations in gamma-glutamyltransferase (GGT) and glutamate dehydrogenase (GDH) serum levels in blood (Morris et al., 1998; Di Menna et al., 2009). There is potential to identify animals that are susceptible to increasing levels of GGT and GDH and through selective breeding, eliminate these animals from breeding herds to decrease the occurrence of facial eczema in future generations.

1.2 GENOTYPE BY ENVIRONMENT INTERACTION

Along with environment, the genetic makeup of an animal or a herd will likely contribute to how well the animals adapt. Often the two interact in a phenomenon known as genotype by environment interaction, in which the differences observed or measured in performance between two or more genotypes changes from one environment to another (Bourdon, 1999). Fescue toxicosis (discussed previously) is an example of a genotype by environment interaction in which in differing environments (i.e. those containing the cultivar versus environments without the cultivar) there are animals that are susceptible to the fescue poisoning and others that are seemingly resistant. There is the potential for re-ranking of the performance of these animals as they are moved from one environment to another.

Changes in elevation can greatly alter how effectively cattle adapt to reduced environmental oxygen. Hypoxia is a condition in which the body (or particular parts) is deprived of adequate oxygen. Hypoxic environments elicit unfavorable response of the pulmonary system. High altitude disease is an illness as per the inability of cattle to adapt to a high altitude environment. It is now well understood through other research efforts that there is a genotype by environment interaction occurring with the disease, since not all animals residing at high altitude

will develop the disease. Pulmonary arterial pressure scores are an indicator for an animal's susceptibility to HAD and will be discussed in more depth in subsequent sections. It has been speculated that animals with high PAP scores at lower altitudes will likely have even higher PAP scores in high altitudes. However, no research has been conducted examining whether animals with low PAP at lower altitudes will also have lower PAP at high altitudes. There is potential for re-ranking of animals for these types of measures as animals are taken from lower to higher altitudes. Additionally, there are many other environmental factors that influence the onset of the HAD in cattle.

SECTION 2: HIGH ALTITUDE DISEASE: ETIOLOGY, PATHOPHYSIOLOGY AND CLINICAL PHENOTYPE

High altitude disease is alternatively termed high mountain disease, dropsy, or fat steer disease and has been reported in beef cattle in the state of Colorado since 1889 and in surrounding states including Wyoming and New Mexico since 1915 (Glover and Newsom, 1917). Occurrences in Utah were not reported until 1920 to 1930 (Hecht et al., 1962). The disease derived its name from the noticeable accumulation of edematous fluid in the "loose tissues of the dependent portion of the trunk, particularly in the region between the forelegs and neck" (Hecht et al., 1962). This fluid accumulation is due to increased vascular hydrostatic pressure and subsequent loss of fluid into the extravascular spaces, such as the pericardium (Holt and Callan, 2007). Initial research related to HAD presented the cause of the disease as exhaustion of the heart muscle associated with a varying degree of dilation and hypertrophy (Glover and Newsom, 1917). High altitude disease is caused by the occurrence of pulmonary arterial hypertension, however they are not one in the same. High altitude disease is said to be an

animal model of hypoxic pulmonary hypertension and may represent a naturally occurring experimental model for heart failure in cattle (Kuida et al., 1963; Newman et al., 2011).

2.1 PULMONARY ARTERIAL HYPERTENSION

2.1.1 Right Heart Failure

Pulmonary arterial hypertension (PAH) is a disease of the small pulmonary arteries, characterized by narrowing of the pulmonary vasculature due to increased size of the arterial adventitia leading to a progressive increase in pulmonary vascular resistance, and consequently increasing right ventricle afterload causing failure of the right ventricle (Humbert et al., 2004). Pulmonary arterial hypertension can be more simply referred to as pulmonary hypertension. Based on a study of pulmonary hypertension in humans, the main vascular changes include vasoconstriction, smooth-muscle cell and endothelial-cell proliferation of the adventitia, and thrombosis (Farber and Loscalzo, 2004). “Cor pulmonale” is a collective term used to describe the conditions of right heart dilation, hypertrophy, and subsequent failure caused by pulmonary hypertension and increased pulmonary vascular resistance (Peek and McGuirk, 2008). In cattle, the causes of the illness are clinically and hemodynamically the counterpart of pulmonary hypertensive heart disease in humans (Hecht, 1956).

2.1.2 Mechanisms of Pulmonary Hypertension

Pulmonary arterial hypertension has a multifactorial pathophysiology, and no one factor or gene will explain all forms and cases of PAH (Humbert et al., 2004). Grover et al. (1963) hypothesized that pulmonary hypertension involved two related processes: (1) a progressive increase in arterial vasoconstriction due partially to vascular smooth muscle hypertrophy, and (2)

obstruction of the pulmonary arteries. Findings from a study by Kuida et al. (1963) gave strong evidence to the thought that pulmonary hypertension in HAD animals resulted from exaggerated hypoxic pulmonary vasoconstriction. The principle factor responsible for pulmonary hypertension in cattle appeared to be increased resistance of blood flow through the lungs as per was reflected by the reduction in cross-sectional area of the pulmonary vasculature (Will et al., 1962; Kuida et al., 1963). Figure 1.1 is a diagram presented by Neary (2013) representing the stiffening, impedance and resistance associated with pulmonary hypertension. This image complements research efforts by Elzinga and Westerhof (1973) and Zuckerman et al. (1992) and Stenmark et al. (1987, 2009).

In humans, there are three plausible mechanisms for developing pulmonary arterial hypertension: hypoxia, anorexigens, and central nervous system stimulants (Farber and Loscalzo, 2004). It was postulated by Alexander et al. (1960) that the pulmonary hypertension response in cattle could be attributed to chronic hypoxia. Will et al. (1975b) brought evidence to this postulation by finding a strong positive relationship between the pulmonary pressure response under acute and chronic hypoxia. These results suggested that acute and chronic hypoxia share a common mechanism in cattle.

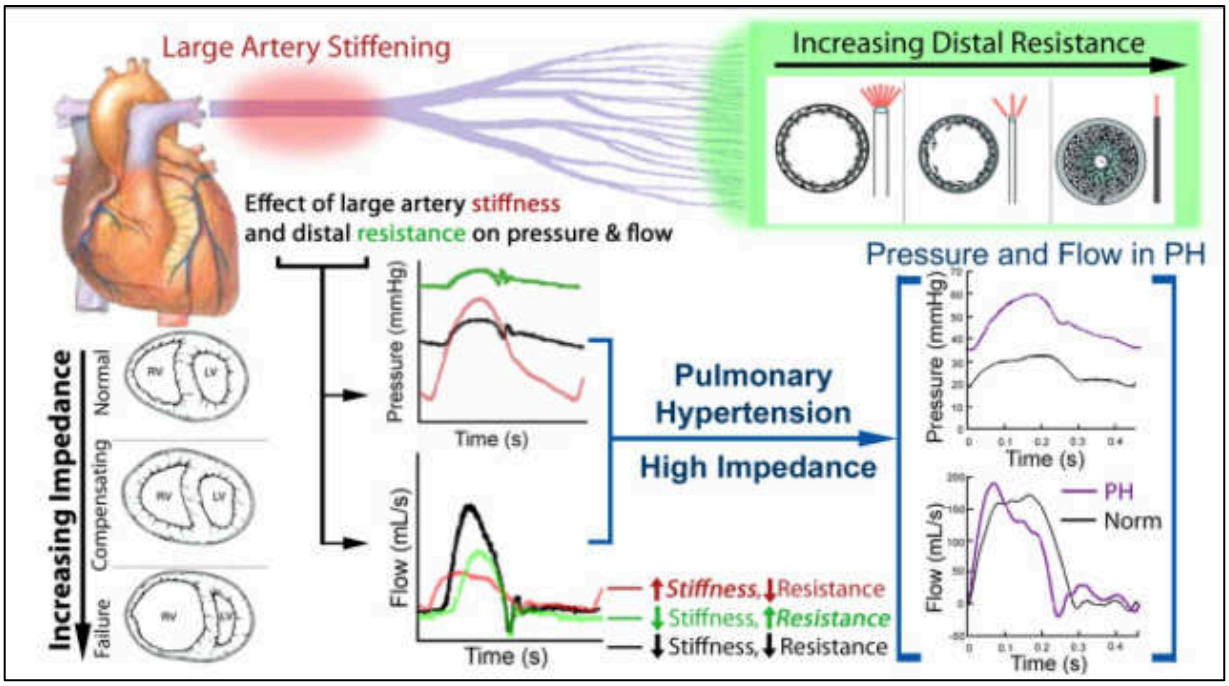

Figure 1.1. Diagram demonstrating the relationship between ventricular work, impedance of flow due to large pulmonary artery stiffening and resistance to flow due to narrowing of the distal pulmonary vessels. Vascular stiffness, due to structure-function changes in the vessel wall elastin, and distal 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, 2013)

2.1.3 Structural Changes in Vasculature

Multiple studies have examined structural changes in the pulmonary arterial vessels and their effect on the presence and persistence of pulmonary hypertension in high altitude cattle (Jaenke and Alexander, 1973; Tucker and Rhodes, 2001; Stenmark et al., 2006). Their findings suggest that chronic hypoxic conditions had an effect on adventitia thickening and increase in the diameter of the pulmonary vessels and development of new vessels (Reeves and Leathers, 1967; Stenmark et al., 1987). It is more clearly understood and accepted that this structural remodeling contributes to right ventricular workload and altered flow dynamics resulting in pulmonary hypertension (Neary et al., 2013). An experiment by Tucker et al. (1975) found a strong correlation ($r = 0.88$) between the amount of medial smooth muscle in the small pulmonary

arteries and the magnitude of pulmonary hypertension in response to chronic hypoxia. From that study, the classification of cattle as 'hyper-responders' was developed based on the amount of medial smooth muscle comprising the small pulmonary arteries and arterioles. Cardiac ventricular ratios revealed a significant right ventricular hypertrophy in the animals at the high altitude. Structural changes have been related to the progressive increase in PAP in calves exposed to high altitude (Jaenke and Alexander, 1973). Based on a comparative evaluation by Tucker and Rhodes (2001), they concluded that cattle with thick-walled pulmonary arteries are hyper-responders at high altitude. They also concluded that young calves were most responsive to high altitude.

A study by Kuriyama and Wagner (1981) examined the effect of collateral ventilation in the presence of high-altitude derived pulmonary hypertension, where as defined by Fessler (2005), collateral ventilation is the ventilation of alveolar structures through passages or channels that bypass the normal airways. They found a correlation between the absence of collateral ventilation and presence of thick walled pulmonary arteries in cattle. They concluded that because cattle lack collateral ventilation, the walls of their vessels were thick at low altitudes and even thicker when these animals were in high altitudes, increasing the development of pulmonary hypertension at high altitude (Kuriyama and Wagner, 1981).

A marked degree of variability can be seen in the magnitude of pulmonary hypertension and degree of right ventricular hypertrophy in mammalian species as a whole and individuals within a species when stimulated under similar conditions (Rhodes, 2005). Treatment goals of PAH are to reduce pulmonary vascular resistance and PAP and thereby reverse the pressure overload on the right ventricle. This effort would be to prevent failure of the right ventricle and ultimately death of the patient (animal) (Stenmark et al., 2009).

Beef cattle producers can attempt to decrease the susceptibility of cattle to HAD by implementing selective breeding strategies. Neary et al. (2013) stated that because of increased genetic selection for various production traits, cattle today have small lungs relative to their body size and metabolic demand. This has the potential to increase their risk of cardiopulmonary disease. However, the study by Neary et al. (2013) examined cattle that were utilized primarily for growth and market performance. In order to support this statement, it would be pertinent to examine and compare different populations of cattle, those selected for post-weaning and carcass performance and those selected more for fertility. There is still much to be learned in the pathogenesis of bovine pulmonary hypertension.

2.2 PULMONARY HYPERTENSION MANIFESTED IN THE DISEASE

2.2.1 Environmental Challenges Associated with High Altitude Disease

High altitude environments were described as the primary factor instigating HAD in cattle (Newsom, 1915; Glover and Newsom, 1918). However, additional factors including micro-climate, season, weed or vegetation exposure, oxygen availability, and management also play crucial roles in the occurrence of the disease.

2.2.1.1 Climate and Season

A study by Jensen et al. (1976) surveyed illnesses and deaths in yearling feedlot cattle at elevations of ≥ 1,600 m. The study found the incidence of death due to HAD was approximately 5.8% of the 1,988 animals necropsied. The study also determined that the malady occurred in all seasons, but was most common throughout the fall and winter (Jensen et al., 1976). Results from Will et al. (1978) determined that environmental cold caused a rise in PAP and vascular

resistance and a fall in arterial oxygen tension. For susceptible animals, PAP scores were found to increase upon exposure to temperatures from 0°C to 5°C. During the first 24 h of cold exposure, a major factor contributing to elevation of PAP was an increase in pulmonary blood flow (Will et al., 1978). When Hereford calves in a controlled temperature setting (14°C to 16°C) were compared to those exposed to cold temperatures (-2°C to 1°C), there was a significant difference ($P < 0.05$) in PAP scores, where with every one degree decrease in temperature, a 1.38-mm Hg increase in PAP would be expected (Busch et al., 1985). They concluded that due in part to cold-induced hypoventilation, mild exposure to cold temperature elicits pulmonary hypertension in normal cattle. Altitude exposure was found to be an additive effect to the responses of cold exposure on PAP scores. Cold exposure was found to increase PAP scores, but the addition of altitude exposure resulted in an increase in PAP over and above what was found with cold exposure alone (Busch et al., 1985).

2.2.1.2 Weeds and Vegetation

Swainsonine is a compound contained in locoweed (genera *Astragalus* and *Oxytropis*) that has been identified as a significantly mediator of HAD in calves at high elevation and may increase the risk of development of HAD (Panter et al., 1988; Holt and Callan, 2007). Calves at high altitude (3,090 m) fed locoweed demonstrated clinical signs of HAD and showed microscopic lesions suggestive of HAD (James et al., 1991). There has been no specific data indicating swainsonine causes pulmonary hypertension and elevation of PAP scores, however it is possible that the effect of swainsonine exposure on development of HAD is due to direct cardio toxic effects combined with hypoxic pulmonary hypertension (Holt and Callan, 2007).

2.2.1.3 Elevation and Oxygen Availability

Changes in elevation and oxygen availability can greatly alter how effectively cattle adapt to environmental changes. A report by Holt and Callan (2007) found that PAP scores increased 1 to 2 mm Hg for every 304.8 m rise in elevation. Will et al. (1975c) found that PAP increased with increasing altitudes of residence and the magnitude of changes in PAP were much less in native cattle than in cattle derived from low altitude production systems. It may not be advantageous therefore to test cattle that are native to high altitude (Tucker and Rhodes, 2001).

Administration of oxygen to animals has shown to alter their reaction to altitude changes. A previous study at altitude (3,048 m) administered 100% oxygen to yearling Hereford steers for 10 minutes and found a prompt fall in mean PAP. However once the oxygen was removed, the pressures increased to their initial values prior to oxygen administration (Will et al., 1962). However, after 15 days exposure to high altitude, no significant decrease in PAP was witnessed in calves when 100% oxygen was administered (Will et al., 1962). Likewise, Alexander et al. (1960) administered 100% oxygen to two hypertensive cattle and witnessed a reduction of PAP scores. Angel and Tyler (1992) stated that prolonged oxygen administration successfully resolved pulmonary hypertension, even when severe chronic bronchitis or emphysema was present.

Hohenboken et al. (2005) stated that the adaptation of animals to a specific environment declines when outside or non-native animals were used for breeding purposes. This is due to the disruption of allele frequencies and gene combinations favorable to production in that local environment (Hohenboken et al., 2005). This may be a fitting preliminary explanation for the differing responses to hypoxia amongst cattle, native versus non-native, and allude to a

relationship with genetics, where offspring from outside breeding sires may not be adequately suited for production in high altitude environments.

2.2.2 HAD – Role of Genetics and Selective Breeding

Susceptibility of cattle to pulmonary hypertension and subsequent high altitude disease is presumed to be in part, genetically controlled (Will et al., 1975a). The PAP score has been estimated to be moderate to highly heritable (0.20 to 0.46), and can therefore be used to accurately predict HAD or pulmonary hypertension susceptibility and to make selection decisions (LeValley, 1978; Enns et al., 1992; Cockrum et al., 2014).

As stated previously, pulmonary hypertension has a potential multifactorial pathophysiology and PAP is a polygenic trait, where not all information for either of these is fully understood (Humbert et al., 2004; Cockrum et al., 2014). Greater insight into the pathogenesis of HAD can be initiated through the identification of candidate genes. Newman and colleagues discovered candidate genes NADH dehydrogenase (ubiquinone) flavoprotein 2 (NDUFV), myosin heavy chain 15 (MYH15), myocardial signaling protein (FKBP1A), and endothelial PAS domain-containing protein 1 (EPAS1) that are possibly involved in pulmonary hypertension (Newman et al., 2011, 2015). Examining the expression levels of these genes can be executed to identify disease processes, physiological, cellular and molecular functions, as well as canonical pathways that may be enhanced in animals exhibiting pulmonary hypertension at high altitudes.

2.2.3 Signs and Symptoms Associated with HAD

Table 2.1 describes clinical signs and symptoms found to be associated with HAD in cattle (Glover and Newsom, 1917; Holt and Callan, 2007; Neary et al., 2013). The list is separated into an ante-mortem category, which describes more visual, non-invasive observations,

and a post-mortem category. The typical course of the disease lasts anywhere from two weeks to three months, with a majority of cattle dying within a month after symptoms were noticed (Glover and Newsom, 1917). Other research has stated the progression of the disease lasts between one and 12 weeks (Pierson and Jensen, 1956). To put HAD in context of other diseases, Neary et al. (2013) reported calves with pneumonia at very high elevations of 2,438 to 3,505 m exhibit signs similar to pulmonary hypertension.

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

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

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

2.2.4 Impact of HAD on the Beef Industry

2.2.4.1 Prevalence of HAD

The incidence of HAD can range from 0.4 to 40%, as reported by (Will et al., 1975a; Salman et al., 1990). One of the most recent reports in 2013 received data from a ranch in southwestern Colorado that had been selecting bulls on low PAP for over 25 years. The study indicated 11.9% (± 0.8) of their calves died or were presumed dead before weaning in autumn from 2006 to 2010 due to a multitude of other factors, including but not limited to environmental conditions, predators, and diseases including HAD. Earliest studies on HAD reported with rises in elevation, the prevalence of the disease increased (Glover and Newsom, 1918).

A recent study by Malherbe et al. (2012) indicated an incidence rate for brisket-like disease in Holstein heifers of 21.8% of all deaths over a 7-year period in Colorado cattle at an elevation of 1,600 m. This is similar to a report by Holt and Callan (2007) with an incidence rate of 25% in the Colorado high country. The lowest reported incidence of HAD was from a survey by the National Animal Health Monitoring System (NAHMS), where the incidence rate was 1 cow per every 200 cows at risk (Salman et al., 1990). The authors did not explain the definition of 'at risk' cattle. Will et al. (1975a) reported HAD incidence in 1975 at 0.5 to 2% of cattle native to 2,133 m. Their reported incidence rates increased to 10 to 40% for low-altitude raised cattle subjected to high altitudes. These findings supported earlier literature by Glover and Newsom (1917) where they found that the disease is far more prevalent in cattle that were transported from low altitudes to high altitudes. "Natural and artificial selection are believed to have minimized the level of pulmonary hypertension in native cattle to high altitude, thus protecting them from high mountain or brisket disease" (Will et al., 1975c). The distinction

between native (born and raised at high altitude) and non-native (born at low altitude and brought to high altitude) cattle appears to be an important factor in the prevalence of the disease.

Pierson and Jensen (1956) and Blake (1968) quantified the incidence of HAD based on age and found that the majority of cases (~75%) occur between birth and 2 years of age, with the incidence dropping to 3% or less in cattle from 2 to 5 years of age (Rhodes, 2005). However, in ages greater than 5, the incidence was reported to rise to 20%. Blake (1968) stated that the incidence of the disease in calves is about two-times as high as cows and bulls, which have approximately equal susceptibility. Evidence of this statement can be found in a Utah Agriculture Experiment Station circular where 397 cases of HAD were reported, of which 269 (~68%) were in calves (Blake, 1968). An explanation for higher susceptibility in calves as opposed to adult cattle has not been presented.

Cattle are thought to be genetically predisposed to HAD with occurrence of the disease dependent on many factors. A previous study examined the differences in PAP over 2 generations of calves from susceptible and resistant parents (Will et al., 1975a). The study found that susceptible calves (those born from susceptible parents), at 10 days of age, had higher PAP at 1,524 m and 4,572 m than the resistant calves (those born from resistant parents). Likewise at 90 days of age, during acute hypoxic conditions of 4,572 m (artificially created in a hypobaric chamber), susceptible calves tended to have higher PAP scores than the resistant calves. At the an elevation of 3,048 m, the study found that all susceptible calves at 124 days of age had developed signs of heart failure (Will et al., 1975a), while none of the resistant calves developed these signs. These results agreed with those of Glover and Newsom (1917) reported many years prior, as they determined that calves sired by low altitude bulls were much more susceptible than those sires by native bulls.

Little is known of breed differences for HAD with the exception of findings from 5 studies. Before a report by Hecht et al. (1962), it was thought that the French breed of cattle Charolais were resistant to the disease because no cases had been reported. The Utah Agriculture Experiment Station echoed this thought in a circular report in 1968 (Blake, 1968). However, this may have been due to the small number of Charolais cattle present in these regions in the 1960s. Holstein cattle were said to be particularly susceptible to high altitude disease (Peek and McGuirk, 2008). Research by Rudolph and Yuan (1966) and Stenmark et al. (1987) confirmed responses to hypoxia in Holstein calves and PAP changes.

2.2.4.2 Economic Impact of HAD

Based on what was presented in the preceding section relative to incidence and prevalence of HAD, the potential economic impact of the disease is large. In a report by the National Animal Health Monitoring System from 1986 to 1988, the cost of deaths of diseased animals was the largest contributor (approximately two-thirds) to the total mean annual cost of disease incidence in Colorado cow-calf herds (Salman et al., 1991b). High altitude disease is one of the primary causes of morbidity and mortality in cattle raised at high altitude, and accounts for significant losses in growth and reproductive performance (Holt and Callan, 2007). In the same report, it was stated that cattle losses due to HAD could be 3 to 5% of the calf crop. The same study estimated that in 2007 on average, HAD accounted for 5% (75,000 cattle) of annual death loss in Colorado, Wyoming, Utah, and New Mexico with those animals having a value of approximately $60 million (Holt and Callan, 2007). Based on a earlier report dating back to 1889, HAD caused an annual loss of approximately 1% of all cattle maintained above an altitude of 2,438 m (Glover and Newsom, 1917).

2.2.5 Management Practices to Avoid HAD

There is no known cure for HAD in cattle; however, treatment options are available to mitigate or decrease the severity of the disease on cattle. Administration of diuretics for decreasing cardiac overload, antibiotics for secondary infections, B-vitamins, and oxygen therapy are a few ways to treat cattle suffering from the disease. Likewise, restrictions on water and salt intake, keeping the animal warm to reduce environmental control, or draining the fluid from the thoracic cavity of the chest are other treatment options available (Tim Holt; personal communication). It is recommended as a preventative measure to use bulls for breeding purposes that have been raised at altitudes of 2,438 m or above (Glover and Newsom, 1917). Some cattle suffer from extreme exertion upon first arrival to high elevations. It has been suggested that more care should be taken in the handling of the animals during the first few weeks of arrival to high altitudes or that animals should be brought to higher altitudes more gradually to lesson the extent of exertion (Glover and Newsom, 1917).

2.3 PULMONARY ARTERIAL PRESSURE: SCORES, GENETICS, AND INFLUENCES

2.3.1 Background Information and Historical Standpoint

The presence of pulmonary hypertension in cattle can be confirmed through the use of PAP testing (Holt and Callan, 2007). Pulmonary arterial pressures are measured in millimeters of mercury (mm Hg), where higher pressures (> 49 mm Hg) are indicative of animals with greater susceptibility to developing pulmonary hypertension and subsequent right heart failure leading to death (Holt and Callan, 2007). As reported in Reeves et al. (1962), Hales first recorded arterial blood pressure measurements in horses in 1733 and the first cardiac catheterization was

performed in horses by Chauveau and Marey in 1861. The first recorded PAP scores in cattle were done by Alexander et al. (1960).

2.3.2 An Invasive Collection Procedure

The current PAP test involves catheterization of the right side of the heart and the pulmonary artery. Per the explanation provided by Holt and Callan (2007), after restraining the animal and creating jugular exposure, a 13-gauge 3.5-in bore needle is used for venipuncture through the skin and into the jugular vein. A catheter is passed through the jugular vein, through the right atrium and right ventricle of the heart, and on into the pulmonary artery. A pressure transducer connected to the catheter captures systolic, diastolic, mean PAP, and wedge pressures. Monitoring pressure changes and characteristics of the pressure wave on a blood pressure monitor gives an accurate assessment of the location of the catheter in the heart. Characteristics of the pressure wave within the pulmonary artery include a low amplitude and moderate frequency. The catheter is then slowly retracted and the needle is removed. See Holt and Callan (2007) for a more detailed description of the procedure involved.

The procedure for collecting PAP scores is invasive and expensive in nature, thus a study preformed by Ahola and co-workers in 2006 examined alternative ways to predict PAP scores in cattle. The study found three blood parameters that were moderately correlated with PAP: packed cell volume ($r = 0.31$), hemoglobin concentration ($r = 0.33$), and red cell distribution width ($r = -0.36$). However, results were inconclusive relative to suggesting an accurate and repeatable alternative method for predicting PAP scores. Likewise, years prior research by Cueva (1967) and Card (1977) looked at blood components in comparison to PAP scores, with results similar to that found by Ahola et al. (2006). Thus, PAP is still the industry's best indicator of an animal's susceptibility to pulmonary hypertension and right heart failure.

2.3.3 Genetics associated with PAP

Any environmental challenge and underlining genetic predisposition of an animal to pulmonary hypertension and HAD will show an altering effect on the PAP scores recorded. As stated previously, PAP testing has been used to confirm pulmonary hypertension in cattle and is used as an indicator trait for HAD selection because of its moderate to high heritability. A high heritability estimate of 0.66 ± 0.21 was reported by LeValley (1978) for PAP in Angus and Hereford cattle. Schimmel (1981) estimated the heritability of PAP as 0.40 ± 0.13 from n = 667 weanling calves from different sire lines at the San Juan Basin Research Center. A heritability estimate of 0.46 ± 0.16 from 489 records was reported by Enns et al. (1992) and in a later study by Shirley et al. (2008), a heritability of 0.34 ± 0.05 was reported from n = 2,305 records. Both of these studies were conducted on the same western Colorado ranch. Heritabilities were also calculated separately for males and females in that population, resulting in estimates of 0.46 ± 0.09 and 0.38 ± 0.07, respectively (Shirley et al., 2008). A sex-specific analysis was conducted more recently on Angus cattle raised at high altitude, where overall heritability estimate of PAP was found to be 0.31 ± 0.03, while heritability estimates for heifers, bulls, and steers (using subsets of data) were 0.21 ± 0.04, 0.38 ± 0.08, 0.20 ± 0.15, respectively (Cockrum et al., 2014). Based on the moderate to high heritability estimates, it seems as though selection of breeding animals based on PAP would be advantageous to reducing the susceptibility to HAD. The report of Enns et al. (1992) made a parallel suggestion.

There are suspect challenges on PAP scores that will be discussed in greater detail in a following section. Controlling or accounting for these factors has the potential to mitigate unfavorable PAP scores. For example, Darling and Holt (1999) found differing correlations in pairwise comparisons of parent-offspring relationships and PAP. The sire-daughter correlation

(0.199) was different from the sire-son correlation (-0.011). However, the dam-daughter (0.108) and dam-son (0.106) correlations were nearly the same. They attributed this to either the maternal effects on the calves or the differing inheritance of PAP for male and female calves, thus suggesting a genetic sex-effect for mode of inheritance. If the correlations between all parent-offspring pairs were the same, this would suggest that PAP is a sex-dependent trait. Also, if the correlation between father-son PAP was equal to zero, this would suggest a sex-linked aspect to the trait. Due to the fact that neither is observed in the work by Darling and Holt (1999), it was suggested that it may be caused by an autosomal gene with reduced penetrance, in which PAP remains at a normal level, even though the genotype suggests an abnormality. Research by Newman et al. (2015) suggests a method for correlating the genotype of the animal in relation to their phenotype PAP.

2.3.4 Factors Influencing PAP Scores

Cattle displaying signs of pulmonary hypertension typically have PAP values > 48 mm Hg (Holt and Callan, 2007). Based on previous findings, normal animals at ≥ 1,524 m should have a mean central venous pressure of 6 to 12 mm Hg, a mean right ventricular pressure of 18 to 30 mm Hg, and a mean PAP between 34 and 44 mm Hg (Holt and Callan, 2007). There are a host of factors that can affect PAP scores in cattle. These include: breed, sex, age, pregnancy status, body condition, concurrent illness, environmental conditions (e.g. temperature), elevation, and genetics (Holt and Callan, 2007). All of these factors must be considered in order to accurately use and understand PAP scores.

2.3.4.1 Breed

High PAP values have been found in all breeds tested and not one breed of cattle appears to be resistant to high-altitude hypoxia (Holt and Callan, 2007). Table 2.2 lists the different cattle breeds that have been PAP tested in previous research (Note: this is in reference to PAP and does not necessarily translate to HAD).

Table 2.2. List of cattle breeds that have been PAP[i] tested and the corresponding citation.

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

[i] Pulmonary arterial pressure

2.3.4.2 Sex

In multiple research efforts, Schimmel and colleagues found opposing correlations for PAP and growth in differing sexes, where heifer pre-weaning growth was positively correlated with PAP but post-weaning growth in bulls was negatively correlated with PAP (Schimmel et al., 1980; Schimmel and Brinks, 1982, 1983). Darling and Holt (1999) found similar results and stated that this could possibly be explained through a differing genetic control of PAP for male and female calves further suggesting genetic (sex-linked) influence. As reported in recent research by Cockrum et al. (2014), yearling PAP scores can be considered two different traits in

heifers and bulls based on the heritabilities of 0.21 ± 0.04 and 0.38 ± 0.08, respectively, and their genetic correlation of 0.64 ± 0.14. These results signify differing inheritance of the trait between heifers and bulls and because they were only moderately to highly correlated, it can be inferred that they can be considered two different traits. Shirley et al. (2008) also found a moderately high genetic correlation (0.64 ± 0.12) between PAP for males and female calves. However, different management of bulls versus heifers and rate of gain requirements play an important role in the differing correlations seen with PAP.

2.3.4.3 Age

Reeves and Leathers (1964) stated that the magnitude of the PAP score in response to hypoxia is dependent upon both the age of the calf and the degree of hypoxia. As a base reference point, Holt and Callan (2007) suggest that cattle older than 12 months of age, with a PAP score less than 41 mm Hg, at an elevation of ≥ 1,500 m are suitable breeding stock for high elevations. On the contrary, they stated that cattle of any age, with a PAP scores > 49 mm Hg, at any elevation are at risk of developing high altitude disease and use as breeding stock at high altitude was not recommended (Holt and Callan, 2007).

The accuracy of the PAP test is less predictable when animals are 12 months of age or less because greater variation is exhibited over time (Holt and Callan, 2007). Reeves and Leathers found a significant increase in PAP during the first 4 weeks of post-natal life of calves at an elevation of approximately 3,350 m (Reeves and Leathers, 1967). Therefore, more fluctuation or variation in PAP scores exist with younger cattle and the predictions for those animals and their susceptibility may be deceptive. In previous research, age at PAP was found to be a significant factor in the analysis ($P < 0.02$) with increasing PAP as age increased (b = 0.0387 mm Hg·d^{-1}; Enns et al., 1992). In relation to both sex and age, Shirley et al. (2008) found

measurements of PAP increased 0.022 ± 0.008 mm Hg·d^{-1} in females, and decreased 0.004 ± 0.01 mm Hg·d^{-1} for males. The difference in the results of Shirley et al. (2008) compared to the earlier studies may be due to the separation of sexes into bulls and heifers and different management for gain. Partitioning the regression of age on PAP by sex could give the results presented by Shirley et al. (2008). Therefore, age at time of PAP measure is an important effect to gauge the potential susceptibility to HAD.

2.3.4.4 Pregnancy Status

Previous studies have found that pregnant cattle susceptible to HAD had an increased PAP compared to those that were not pregnant (Moore et al., 1979). There is potential for death to occur in cows residing at high altitudes during the postpartum period due to right heart failure because of pulmonary hypertension that developed during the pregnancy (Moore et al., 1979).

2.3.4.5 Concurrent Illness

Table 2.3 lists some infectious and noninfectious respiratory diseases that can predispose cattle to pulmonary hypertension (Holt and Callan, 2007). Many of the infectious agents fall under the umbrella of Bovine Respiratory Disease (BRD). Gram-negative sepsis also has the ability to cause an elevation in PAP scores and affect an animal's susceptibility to pulmonary hypertension (Tikoff et al., 1966; Reeves et al., 1972, 1973). It was postulated by Holt and Callan (2007) that treating cattle with flunixin meglumine may be clinically helpful in blocking the effect of endotoxin on pulmonary hypertension.

Table 2.3. List of infectious and noninfectious agents associated with respiratory diseases predisposing cattle to pulmonary hypertension.

Infectious	Noninfectious
Bovine Viral Diarrhea Virus (BVDV)	Lung abscess
Infectious Bovine Rhinotracheitis (IBR) [i]	Lung worm
Parainfluenza Type 3 (PI3) [i]	Migrating larva of intestinal parasites
Histophilus somni [i]	Asthma
Pasteurella multocida [i]	Reticuloperitonitis/pleuritis
Mannheimia hemolytica [i]	

[i] Associated with Bovine Respiratory Disease (BRD)

2.3.5 Environment and Economic Impact of PAP testing

The year in which PAP was measured has also been observed as a significant factor or effect on PAP taken on weaning calves (Schimmel, 1981). Age of the dam has been reported to be a non-significant factor ($P > 0.7$) influencing PAP scores, but results of that study suggest there may be both individual and maternal influences, such as additive or permanent environment maternal influences, on PAP (Shirley et al., 2008).

Pulmonary arterial pressures can be used as an indicator for HAD, but at an additional cost to producers. A study by Salman et al. (1991a) showed that pregnancy examinations, breeding soundness examinations on bulls, brucellosis and campylobacteriosis vaccinations, and PAP testing accounted for over 90% of the expenditures for preventive veterinary services. Although these account for additional costs to beef production systems, it would be of benefit to use resources and preventative services to decrease the economic impact HAD.

SECTION 3: GROWTH TRAITS

3.1 INFLUENCES ON CATTLE GROWTH PERFORMANCE

Weight traits are important to the profitability of the beef industry. In 1993, economic losses in the United States from decreased calf weaning weights were estimated at $255 million annually (Hoveland, 1993). Therefore, examination of growth traits in relation to HAD and pulmonary hypertension is critical in the proper prevention, diagnosis, and treatment of affected animals. One postulated causative factor of HAD is rapid growth rate. Greater rates of growth demand constant movement of blood through the circulatory system, which subsequently increases the work load of the ventricles of the heart, leading to heart failure in susceptible animals (Jensen et al., 1976). Meyer (1992b) stated that in order to achieve optimum progress in a selection program, it is necessary to take into account both the direct and maternal components of a trait. Thus, both maternal and non-maternal environmental influences that exist will be examined more closely and how alterations on growth performance can impact the susceptibility of cattle to HAD.

3.1.1 Direct Influence on Growth

The additive direct genetic component is defined as the effect of an individual's genes on its performance. Growth in cattle can be affected by this direct genetic component and breeding and selection decisions can account for this effect (Bourdon, 1999). Setting maternal and non-maternal environmental influences aside, the direct effect of growth reflects the genetic merit of an animal for its growth performance. This allows for the comparison of an animal to its contemporaries, examining the underlying genetics that sets each animal apart from one another. The genetics originate from the genetic contribution of both the sire and the dam. If an animal is selected, for example, for high post-weaning growth based on a superior EPD of his sire, then

regardless of the environmental influences, on average that animal is expected to perform superior than his contemporaries for post-weaning gain.

3.1.2 Maternal Influence on Growth

The maternal component of a trait is defined by Bourdon (1999) as the effect of genes in the dam of an individual that influence the performance of the individual through the environment provided by the dam. The dam largely influences both birth weight and weaning weight of the calf. The maternal contribution to these traits comes from: milking ability, mothering ability, extra-chromosomal inheritance, and uterine environment (Meyer, 1992a). It has also been stated that accuracy of selection can be increased by accounting for maternal effects (Robison, 1981).

Alternatively, the dam has less influence on the outcome of yearling weight and post-weaning gain traits in cattle. This concept was reiterated by Waldron et al. (1993) in which they stated that within particular models and herds, maternal effects decreased in importance with time after weaning. However, previous studies, including the current study, evaluated the maternal influence of the dam on post-weaning growth traits through heritability estimates and genetic correlations. It would be beneficial to understand more clearly the effects the dam has on post-weaning growth, whether it be additive or residual permanent environmental influence. Post-weaning gain maternal heritabilities have been found to be lowly (0.01) to moderately (0.20) heritable (Garrick et al., 1989; Mackinnon et al., 1991). Due to these estimates, it appears that some genetic progress can be made with regards to the maternal influence of post-weaning traits. A compiled list of results in relation to use of maternal effects on pre- and post-weaning growth traits can be found in Table 2.4.

3.1.3 Environmental Influence on Growth

The environment reflects anything outside of the direct genetic and maternal factors that can influence the phenotypic outcome of an animal. Some environmental influences affecting growth in cattle include: micro-climate and altitude, management, illness or disease. Previous research by Will et al. (1962) reported differences in the average gain in body weight of cattle at high altitudes (3,048 m) compared to those at lower altitudes (1,524 m). The study found an average weight gain of each animal during the six month time period to be 45 kg for the high altitude group and 102 kg for the low altitude control group, showing a vast difference in gain (Will et al., 1962). Also, results from Williams et al. (2012) suggested that post-weaning gain may be more strongly affected by altitude than weaning weight from an additive genetic point of view. These factors may be of particular interest to feedlot producers raising cattle at high altitudes, where post-weaning weight gains are paramount. Thus, Williams and colleagues studied the genetic correlations between the same post-weaning traits expressed in two different environments (high verses low altitude). The study examined weaning weight (WW) and post-weaning gain (PWG). Correlations of 0.74 and 0.76 for WW direct and PWG, respectively, were found when comparing high altitude verses low altitude. These results indicated that WW and PWG measured at low and high altitudes should each be considered two different traits. However, a large limitation to this study was the researcher's assumptions on the location of the cattle (low verse high altitude) when performance was measured. Assumptions were made solely based on zip codes, ignoring the potential that the zip codes may reflect ranches addresses and not the actual residence of the cattle (Williams et al., 2012). Likewise, this research discussed that a genetic correlation of 0.75 between WW maternal in high versus low altitude implied that the ability of a dam to produce milk for her calf changes based upon the altitude where she might

be in production (Williams et al., 2012).

Some of the major management factors that have the potential to effect growth performance are supply and access to food and water. These management factors are important because scarcity of resources may limit the animals' intake and growth potential. For example, results of a study by Mackinnon et al. (1991) on growth in tropical cattle support the idea that animals that have low maintenance requirements and gain better during the dry season, also have low growth potential and therefore poorer growth in more favorable nutritional environments. This is also an example of a genotype by environment interaction. They then discuss that when selecting for rapid growth rate, focus on growth should be in periods when nutrition is least limiting.

In a previous section, we discussed the environmental influences on, and genetics of, disease susceptibility. There we discussed how the illness fescue toxicosis results in poor animal gains, excessive salivation, and reduced rate of consumption (Stuedemann and Hoveland, 1988). Previous studies have suggested that for each 10% increase in infestation of endophyte infected fescue, there was a 0.045 $kg \cdot d^{-1}$ decrease in steer ADG (Crawford et al., 1989).

3.2 STATISTICAL ESTIMATES OF GROWTH TRAITS

Genetic correlations can reveal much about the relationships, or lack thereof, between traits of interest. Strong correlations, both positive and negative, reveal that genetic change in one trait may result in change of another trait. An example of this in relation to direct and maternal WW effects is echoed by Waldron et al. (1993), in which they stated that the stronger negative genetic correlation between direct and maternal WW suggests that cattle that are

genetically superior for weight at weaning are, on average, genetically inferior for the maternal genetic component of weight.

Many studies have researched heritability estimates and genetic correlations on performance traits, such as birth weight (BW) and WW, in a range of cattle breeds. Table 2.4 was a compiled list of direct and maternal heritabilities, and correlations amongst them for the performance traits BW, WW, yearling weight (YW), and PWG. The breeds of cattle studied were also listed, unless unspecified by the research reports. Table 2.5 represented a compiled list of genetic correlations between performance traits BW, WW, YW, and PWG from two-trait and multi-trait models. This table helps portray the relationship between these performance traits and inference on what weight can be expected from an animal given its weight at a previous time period. For example, the correlation between WW and YW is high (0.68 to 0.93) and therefore it can be inferred from this correlation that if an animal has a high weight at weaning, one would expect them to also have a high yearling weight (Koots et al., 1994; Bennett and Gregory, 1996). Few studies have examined PWG performance and its relation to other growth traits, so it would be valuable to examine this trait more extensively in this thesis.

Table 2.4. Compiled list of heritabilities (direct & maternal) and genetic correlations from single-trait analyses previously reported in research of cattle.

Trait	Reference	h^2	m^2 [i]	r [ii]	Breed [iii]
Birth Weight					
	Trus and Wilton (1988)	0.37	0.13	-0.34	Angus
	Brown et al. (1990)	0.42	0.22	-0.12	Angus
	Mackinnon et al. (1991)	0.61	0.11	0.01	Zebu-cross
	Meyer (1992c) [iv]	0.34	0.10	0.27	Angus
	Meyer (1992c) [iv]	0.36	0.07	0.28	Angus
	Robinson (1996)	0.44	-	-	Angus
	Shirley et al. (2008)	0.45	0.14	-0.12	Angus
Weaning Weight					
	Skaar (1985)	0.24	0.18	0.16	Angus
	Brown et al. (1990)	0.63	0.16	-0.36	Angus
	Meyer (1992c) [iv]	0.19	0.18	0.20	Angus
	Meyer (1992c) [iv]	0.20	0.14	0.23	Angus
	Waldron et al. (1993)	0.12	0.28	0.04	
	Koots (1994)	0.07	0.08	-	Angus
	Eler (1995)	0.13	0.13	-0.32	Nelore
	Robinson (1996)	0.29	0.14	-0.52	Angus
	Speidel et al. (2006)	0.26	0.14	-0.36	Red Angus
	Shirley et al. (2008)	0.16	0.26	-0.44	Angus
	Williams et al. (2012)	0.26	0.12	-0.34	Angus
Yearling Weight					
	Mackinnon et al. (1991)	0.25	0.20	0.01	Zebu-cross
	Meyer (1992c) [iv]	0.32	0.06	0.45	Angus
	Meyer (1992c) [iv]	0.33	0.04	0.49	Angus
	Waldron et al. (1993)	0.30	0.08	0.04	-
	Eler (1995)	0.16	0.10	0.09	Nelore
	Robinson (1996)	0.34	0.13	-0.73	Angus
Post-Weaning Gain					
	Garrick et al. (1989)	0.26	0.01	-0.28	Simmental
	Mackinnon et al. (1991)	0.26	-	-	Zebu-cross
	Koots (1994)	0.52	-	-	-
	Robinson (1996)	0.29	-	-	Angus
	Williams et al. (2012)	0.19	-	-	Angus

[i] Maternal heritability

[ii] Genetic correlation coefficient between direct and maternal

[iii] Blank space signifies unspecified breed

[iv] Estimates dependent on model ran in analysis

Table 2.5. Genetic correlations from two-trait and multi-trait analyses between pre- and post-weaning growth performance in cattle.

Traits	Reference	r [i]	Breed [ii]
Birth Weight with Weaning Weight			
	Mackinnon et al. (1991)	0.57	Zebu-cross
	Iloeje (1986)	0.81	Zebu
	Eler et al. (1995)	0.23	Zebu
	Robinson (1996)	0.61	Angus
	Bennett and Gregory (1996) [iii]	0.52	Composites
	Bennett and Gregory (1996) [iv]	0.67	Composites
Birth Weight with Yearling Weight			
	Mackinnon et al. (1991)	0.47	Zebu-cross
	Koots (1994)	0.38	-
	Robinson (1996)	0.48	Angus
	Bennett and Gregory (1996) [iii]	0.47	Composites
	Bennett and Gregory (1996) [iv]	0.65	Composites
Birth Weight with Post-Weaning Gain			
	Mackinnon et al. (1991)	0.15	Zebu-cross
	Koots (1994)	0.23	-
Weaning Weight with Yearling Weight			
	Mackinnon et al. (1991)	0.84	Zebu-cross
	Koots (1994)	0.68	-
	Eler et al. (1995)	0.74	-
	Robinson (1996)	0.74	Angus
	Bennett and Gregory (1996) [iii]	0.87	Composites
	Bennett and Gregory (1996) [iv]	0.93	Composites
Weaning Weight with Post-Weaning Gain			
	Mackinnon et al. (1991)	0.02	Zebu-cross
	Koots (1994)	0.07	-
Yearling Weight with Post-Weaning Gain			
	Mackinnon et al. (1991)	0.43	Zebu-cross
	Koots (1994)	0.49	-

[i] Genetic correlation
[ii] Blank space signifies unspecified breed
[iii] Purebred population
[iv] Composite population

3.2.1 Effect of Data and Pedigree Structure on Statistical Estimates

Numerous studies have reported large, negative genetic correlations between direct and maternal effects on weight traits in cattle. Possible reasons for the large, negative estimates for direct-maternal correlations are the pedigree relationships, experimental design, size of the data, or bias due to some missing component (Meyer, 1992a). An example of this can be found in a study of the effect of genetic relationships, number of offspring per dam, and influence of proportion of dams with recorded performance (Maniatis and Pollott, 2003). Results suggested that the number of progeny per dam and the proportion of dams with recorded performance considerably influences parameter estimates of heritability and correlations. Maniatis and Pollott (2003) found moderate to large, negative genetic correlations (-0.46 to -0.99) between direct and maternal early weight traits that resulted from data/pedigree structure, where their experimental data structure consisted of only 10% of dams had records. As the data structure increased to 50% of the dams had records, the severity of the negative genetic correlations decreased (-0.35 to -0.51). The range in correlations was also dependent upon the number of offspring recorded for her dam, where as the number of offspring per dam increased (1.5 average progeny per dam to 7.0 average progeny per dam), the correlation increased (-0.51 to -0.35, respectively). Outcomes such as these can significantly alter the interpretation of the results and conclusions of research. Knowledge on ways in which experimental design, data size, etc. affects the parameter estimates and analyzing how these change results is pertinent for interpretation purposes.

3.3 CORRELATION BETWEEN GROWTH AND HAD SUSCEPTIBILITY

Determining correlations between PAP and growth traits are especially important because the genetic merit (i.e. EPD) for BW, WW, and YW have been increasing at a rate of 0.04, 0.6, and 1.1 $kg \cdot yr^{-1}$, respectively, over the last 41 years in Angus (American Angus Association, 2015). This would suggest that there is continually increasing progress being made in these weight traits.

Very few studies have evaluated the relationship between PAP and other performance traits. Table 2.6 outlines the results of two studies reporting the genetic correlations between PAP and BW, and PAP and WW. The results of these studies have great differences in correlations, and their conclusions. For example, Shirley et al. (2008) reported moderately, positive genetic correlations between PAP and BW direct (0.49 ± 0.12) and PAP and WW direct (0.51 ± 0.18) for cattle raised at an elevation of 1,981 m. The conclusions from Shirley et al. (2008) were that "selection for growth based on performance recorded at a low altitude would be expected to increase PAP scores and susceptibility to brisket disease at high altitude" in Angus cattle, as well as, "greater PAP scores did not appear to be adversely phenotypically associated with WW". From these results it can be inferred that as PAP increases, one would expect BW (or WW) to increase, or alternatively if BW or WW increases PAP would be expected to increase.

Table 2.6. Research findings on genetic correlations between PAP[i] and respective growth traits in cattle.

Trait	Reference	r [ii]
Birth Weight		
	Schimmel (1981)	-0.43 ± 0.29
	Shirley et al. (2008)	0.49 ± 0.12
Weaning Weight		
	Schimmel (1981)	0.09 ± 0.29
	Shirley et al. (2008)	0.51 ± 0.18
Yearling Weight		
	Schimmel (1981)	-0.75 ± 0.65

[i] Pulmonary arterial pressure
[ii] Genetic correlation

Alternatively, Schimmel (1981) found a moderate, negative genetic correlation between PAP and BW (-0.43 ± 0.29) for cattle raised at an elevation of approximately 2,400 m. Their conclusions were that PAP was a distinctly different trait and subject to much additive genetic variance. As well, much progress could be made in the reduction of HAD when PAP is included in the selection program (Schimmel, 1981). The negative genetic correlation found between YW and PAP (-0.75 ± 0.65), along with the heritability estimate (0.24 ± 0.20) suggested that it would be possible to make improvement in YW in a selection program while also increasing resistance to HAD. Therefore, selection intensity on performance does not need to be reduced in order to obtain bulls capable of surviving in hypoxic environments.

Other work by Schimmel and colleagues showed that PAP scores are positively correlated with pre-weaning performance in heifer calves and negatively correlated with post-weaning performance in feedlot bulls (Schimmel et al., 1980; Schimmel and Brinks, 1982, 1983). This again lends to the idea of sex being an influencing factor on PAP scores. Fitting a sex effect within the analysis would be able to explain some of the variation observed in the PAP scores. Previous reports also suggested that correlations between growth traits and PAP were

sensitive to age and season in which PAP was measured (LeValley, 1978; Schimmel, 1981; Shirley et al., 2008). It is important to consider the fact that cattle in these studies were subjected to different environments and the correlations gained will be influenced by those environments. Therefore, it is important to be mindful of these factors when analyzing genetic correlations between PAP and other traits.

Much can be said and interpreted from the results of previous literature. However, more research is needed to determine the genetic relationships between growth performance and PAP, since previous research has yielded opposing results relative to growth. Increasing our knowledge on how selecting for more favorable, lower PAP influences growth performance would be of benefit to those in high altitude regions.

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CHAPTER 3

FACTORS INFLUENCING PULMONARY ARTERIAL PRESSURE IN CATTLE: A RETROSPECTIVE STUDY OF THE SAN JUAN BASIN RESEARCH CENTER 4-CORNERS BULL TESTS

SUMMARY

High altitude disease (HAD) in cattle, commonly known as brisket disease, typically occurs at elevations ≥ 1,500 m. The incidence of HAD ranges from 0.5 to 5% in cattle native to high elevation, while in non-native cattle this increases to a range of 10 to 40% and is often fatal. Identifying tolerant breeding stock to decrease morbidity and mortality rates due to the disease will improve profitability of high elevation beef production systems. Pulmonary arterial pressure (PAP) is a tool used as an indicator of an animal's susceptibility to HAD and has been shown to be moderately to highly heritable (0.20 to 0.46). The objective of this study was to identify significant genetic and environmental factors influencing PAP scores and to evaluate breed differences in PAP scores. Data consisting of birth year, pen, breed, yearling age, ADG and PAP were obtained from the San Juan Basin Research Center, 4-Corners Bull Test center located in Hesperus, Colorado (elevation 2,316 m). A subset of 2,041 bull records with PAP scores from 1983 to 2005 was used for this study. Fourteen breeds were represented in over 14 years of data. Using an ANOVA approach, we found that ADG ($P > 0.05$) did not account for significant variation in PAP score and was therefore removed from the model in subsequent analyses. Analyses revealed that with each day increase in yearling age, PAP score increased by 0.03 mm Hg ($P < 0.01$). The results also indicated that breed was an important factor influencing PAP scores ($P < 0.001$). Using a least-squares approach, we found an estimated 13.8 mm Hg range in

PAP between breeds, where Angus x Gelbvieh bulls had the lowest adjusted PAP and Simmental had the highest. Making selection decisions based on breed for high elevation beef production systems could be helpful in reducing the incidence of HAD.

INTRODUCTION

High altitude disease (HAD), commonly known as brisket disease, has been a concern for cattle producers within the Rocky Mountain region for approximately a century. The disease is characterized by the accumulation of edematous fluid in the tissues covering the parasternal muscles, also known as the brisket. This fluid accumulation is due to increased vascular hydrostatic pressure and subsequent loss of fluid into the extravascular spaces, such as the pericardium (Holt and Callan, 2007). High altitude disease has been found to occur in cattle residing at elevations of ≥ 1,500 m with the condition resulting in poor performance and often death.

A continual hardship for beef producers is the economic losses associated with disease and the subsequent death of their cattle (Salman et al., 1991). It was estimated that in 2007, on average HAD accounted for 5% (or 75,000 head) of annual death loss in Colorado, Wyoming, Utah, and New Mexico, at a value of approximately $60 million (Holt and Callan, 2007). Finding a resolution or method of predicting the occurrence of HAD in cattle is a necessity for producers in high elevation regions.

An indicator trait for HAD is pulmonary arterial pressure (PAP; Holt and Callan, 2007). A PAP score reflects an animal's ability to adapt to high-elevated regions and is measured in millimeters of mercury (mm Hg). According to Holt and Callan (2007), cattle over 12 months of age with PAP scores < 41 mm Hg are suitable for breeding stock in high elevation production

systems and have a reduced risk for developing HAD. Alternatively, cattle at any age, and residing at any elevation with a PAP score > 49 mm Hg, are said to be not suitable for breeding stock at high elevations (Holt and Callan, 2007). Pulmonary arterial pressure has been determined to be a moderate to highly heritable trait (0.20 to 0.46), and therefore useful in breeding decisions (Enns et al., 1992; Shirley et al., 2008; Cockrum et al., 2014).

The incidence of HAD in cattle appears to depend on genetic selection pressure against elevated PAP scores (Enns et al., 1992). For animals native to high elevation, the incidence of HAD ranges from 0.4% to 5% with incidence rates in non-native cattle reported as increasing to 10% to 40% (Will et al., 1975; Rhodes, 2005; Holt and Callan, 2007; Neary et al., 2013). The ability to identify animals less susceptible to HAD and ensuing right heart failure is of economic significance to beef production systems. This is true not only in the Rocky Mountain region in North America, but also all high elevation regions globally.

The objective of this study was to evaluate the genetic and environmental factors influencing PAP. As well as, to determine if any breed differences in PAP existed using historical bull test data from the San Juan Basin Research Center 4-Corners Bull Tests in the southwest region of Colorado.

MATERIALS AND METHODS

Data. Historical records were obtained from the 4-Corners Bull Test located at the San Juan Basin Research Center (SJBRC), near Hesperus, Colorado at an elevation of 2,255 m. The data spanned the years 1983 to 2005 and consisted of observations on birth year, pen, breed, yearling age, ADG, and PAP. No more than 6 bulls were allowed per pen. Bull's yearling ages ranged from 204 to 444 days, with a mean of 299 days of age. Testing rules and procedures

stated that bulls were required to have birth dates between January 1st and May 1st in that year of testing (SJBRC, 1999). The original data included bulls of 21 breeds; however, breeds represented by less than 5 bulls with PAP scores were omitted from the analyses.

The final data contained 2,041 records of fourteen breeds of cattle including: Angus, Angus x Gelbvieh crosses, Charolais, Composite, Gelbvieh, Hereford, Limousin, Maine-Anjou, Polled Hereford, Red Angus, Salers, Simmental, and System1 composites. The System1 composite breed was created through the mating of three existing composites of MARC III, CASH, and RX3. The data also contained breeds designated as "other" and "unknown". Since information from these breed categories is not useful to formulating conclusions, they were excluded from the analyses.

Pulmonary Arterial Pressure (PAP). These measurements were available for 14 years of the test; specifically, 1983, 1989, and 1993 to 2005, excluding 2003. The mean PAP score was 45 ± 12.8 mm Hg, with a minimum 29 mm Hg and maximum 145 mm Hg. No criterion for PAP was set for incoming bulls, however generally, PAP scores greater than 50 were considered high (SJBRC, 1999). Pulmonary arterial pressure scores were taken at the end of the testing period, when the bulls were approximately 1 year of age.

Bull Test. Cattle performance testing started in the fall of 1949, when the Four Corners Beef Cattle Improvement Association initially described performance testing rules and procedures. Bulls were annually consigned to the 4-Corners Bull Test center from various breeders in the Rocky Mountain region. The testing period for bulls was originally a 21-day warm-up period, followed by 112 days on test. Weights were recorded at 28-day intervals. However, over the years, test length varied with the tests lasting between 84 d and 140 d. Performance tests ended around yearling age of the bulls. Rations for bulls consisted of feeds

most suitable for maximizing the expression of genetic differences in growth, where the TDN level was 65 to 70% (SJBRC, 1999). Breeders had the option to retain their best performing bulls from the bull tests or to sell their bulls to other breeders in the rocky mountain region. Although information on target ADG was not available for the 4-Corners Bull Tests, typical bull tests target an ADG of 1.5 $kg \cdot d^{-1}$.

Statistical Analysis. The CAR package in R statistical software was used for analysis of variance estimations (R Development Core Team, 2012). The model used to test for significant influence on yearling PAP scores was:

$$PAP = Birth\ Year + Pen + Breed + Yearling\ Age + ADG + error$$

Yearling age was measured in days and used as a covariate in the model. After preliminary analyses, ADG was found to not be a significant predictor of PAP score ($P > 0.05$) and was therefore removed from the model and subsequent analyses (Table 3.1). Pen was used as a proxy for contemporary group (CG) effect. Home ranch effects, such as "breeder" or "ranch", were not included as an adjustment in the definition of CG because of the ambiguity of the locations the bulls originated.

Table 3.1. Analysis of variance results for influential factors predicting PAP scores in the 4-Corners Bull Test bulls (n = 2,041).

Source of Variation	Sum Squared	Degrees of Freedom	F Value	*P* (>F)
Birth Year	11779	12	6.262	0.000[a]
Pen	11819	44	1.714	0.003[b]
Breed	13993	13	6.867	0.000[a]
ADG	229	1	1.464	0.226
Yearling Age[i]	1116	1	7.120	0.008[b]
Residuals	268045	1710		

Within a row, means without a common superscript differ (P < 0.05).

[a] $P < 0.001$

[b] $P < 0.01$

[i] Used as a covariate

RESULTS AND DISCUSSION

The sources of variation birth year, pen, breed, and yearling age effects on yearling PAP used in the analysis of variance were all significant ($P < 0.01$) predictors of PAP (Table 3.2). Average daily gain was a non-significant predictor of PAP score ($P > 0.05$; Table 3.1). Typically superior bulls from each ranch were consigned to the 4-Corners Bull Test center. This may explain why ADG was not a significant source of variation in this study. The regression of PAP score on yearling age yielded a regression estimate of 0.03 ± 0.01, indicating that with each day increase of yearling age, a 0.03 mm Hg increase in PAP score was expected ($P < 0.001$). Given this coefficient and range in yearling ages of the bulls, an increase in PAP of 7.2 mm Hg would be expected from the youngest bulls 204 days of age to the oldest at 444 days of age. The solutions for birth year had a range of 7.7 mm Hg. Similarly, the effect of pen (CG proxy) had a range in PAP of 12.5 mm Hg, within the 44 pens represented in the data.

Table 3.2. Analysis of variance results for significantly influential factors predicting PAP scores in the 4-Corners Bull Test bulls (n = 2,041).

Source of Variation	Sum Squared	Degrees of Freedom	F Value	*P* (>F)
Birth Year	11588	13	6.108	0.000[a]
Pen	12423	44	1.935	0.000[a]
Breed	13554	13	7.145	0.000[a]
Yearling Age[i]	1121	1	7.679	0.006[b]
Residuals	287337	1969		

Within a row, means without a common superscript differ (P < 0.05).
[a] $P < 0.001$
[b] $P < 0.01$
[i] Used as a covariate

Breed was found to be a significant source of variation ($P < 0.001$) influencing PAP scores for bulls developed at high altitude at the 4-Corners Bull Test center (Table 3.2). There was a 13.8 mm Hg range between breeds with the lowest adjusted PAP estimate to those with the

highest adjusted PAP (Table 3.3). Angus x Gelbvieh bulls were found to have the lowest adjusted PAP scores of all breeds, rendering them potentially less susceptible to development of HAD and right heart failure. Angus is a widely used breed of cattle across the United States in both high and low elevations and they had relatively high PAP scores, which were also noted in Table 3.3. This would suggest that crossbreeding between Angus and Gelbvieh cattle might be influential in reducing susceptibility to HAD. Simmental bulls were found to have the highest adjusted PAP values of all breeds compared. Although this data appears to estimate Simmental cattle as potentially more susceptible to development of HAD, this may be due to sample size, as well as may be breeder dependent as Simmental cattle are from Bern, Switzerland and expected to be adapted to high elevation (American Simmental Association, 2015). Owner information on Simmental bulls consigned to the 4-Corners Bull Test center was scarce. Only 11 bulls came from 4 different owners, where the owners of the remaining 72 bulls were unknown. The number of different owners can substantially impact the estimates. More data would be necessary to state strong conclusions about these breed differences in PAP. Also important to be noted is that Gelbvieh bulls had the lowest raw mean PAP values of all breeds. This lends to the idea that as Angus cattle have relatively high PAP, Gelbvieh have low PAP scores in these data, the heterosis from cross-breeding may allow for better acclimation to higher altitudes.

Table 3.3. Results of model means and coefficients for pulmonary arterial pressure (PAP) by breed in the 4-Corners Bull Test bulls (n = 2,041).

Breed	n[i]	Raw Mean	Estimate	Standard Error
Angus x Gelbvieh	10	44.0	41.3	5.5
Angus	448	47.7	8.0	4.1
Charolais	282	45.1	8.3	4.3
Composite	296	43.0	4.0	4.3
Gelbvieh	106	37.6	8.3	6.5
Gelbvieh x Hereford	7	46.0	9.6	4.4
Hereford	518	42.7	3.4	4.2
Limousin	52	43.8	6.9	4.6
Maine Anjou	5	47.2	9.9	7.0
Polled Hereford	114	42.3	5.0	4.2
Red Angus	256	46.7	11.3	4.2
Salers	12	39.5	0.5	5.6
Simmental	83	53.1	13.8	4.5
System 1	216	46.9	10.3	4.3

[i] Number of cattle in each breed group

Limited research has been conducted that compares any cardiopulmonary physiological differences between cattle breeds (Hultgren et al., 1963; Jaenke and Alexander, 1973; Malherbe et al., 2012). Additional research may help explain the differences observed in PAP scores between breeds. However, high PAP scores have been found in all breeds tested and not one breed of cattle appears to be resistant to high-altitude hypoxia (Holt and Callan, 2007). Before a report by Hecht et al. (1962) examining the occurrence of HAD in the French breed of cattle Charolais, it was originally thought that this breed was resistant to the disease because no incidences had been reported prior. The Utah Agriculture Experiment Station echoed this thought in a circular report in 1968 (Blake, 1968). However, this may have been due to the small number of Charolais cattle present in those regions in the 1960s. In a 50th year anniversary report about the beef cattle breeding at the 4-Corners Bull Test center, it was noted that significant line and breed differences in PAP values were obtained from previous research efforts not

specifically listed (SJBRC, 1999). To our knowledge, there has been no previous information reported regarding breed differences in PAP. Further research should be conducted to determine more extensively the factors that influence incidence of HAD and PAP over a larger population of cattle in regards to age, sex, weight, and breed.

CONCLUSIONS

The results of this study suggest that factors such of year of birth, pen, breed, and age were significant sources of variation in predicting PAP scores for the 4-Corners Bull Tests. The results suggest that appropriate breed selection based on reduced PAP scores could be helpful in reducing the susceptibility of cattle to HAD.

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CHAPTER 4

HERITABILITIES AND GENETIC CORRELATIONS BETWEEN PULMONARY ARTERIAL PRESSURE AND PERFORMANCE TRAITS IN ANGUS CATTLE MANAGAED AT HIGH ALTITUDE

SUMMARY

The risk of high altitude disease (HAD) in cattle can be measured by pulmonary arterial pressure (PAP). Due to moderate to high heritability estimates (0.20 to 0.46), PAP provides a means to select breeding cattle so as to reduce the prevalence of the disease in subsequent generations. The objective of this study was to estimate heritabilities and genetic correlations between yearling PAP scores (n = 5,776) and performance traits using data from the John E. Rouse Colorado State University Beef Improvement Center (CSU-BIC) Angus herd (n = 8,718). We hypothesized that little to no genetic relationship exists between PAP and birth weight (BW), weaning weight (WW; direct and maternal components), yearling weight (YW; direct and maternal components), and post-weaning gain (PWG). Selection for herd bulls from within the herd required a PAP score of 45 mm Hg or lower, given other selection criteria were achieved. Outside AI sires were not PAP tested an therefore, were introduced with little knowledge of high altitude adaptability. Performance traits routinely recorded included BW (n = 8,695), WW (n = 8,010), YW (n = 5,580) and PWG (n = 5,453). Single-trait, 2-trait, and multi-trait analyses were conducted using an animal model. Heritability estimates for PAP (0.26 ± 0.03), BW (0.58 ± 0.02), and WW direct (0.41 ± 0.04) and maternal (0.28 ± 0.03), YW direct (0.48 ± 0.04) and maternal (0.23 ± 0.02), and PWG (0.12 ± 0.02) appeared to be within ranges reported in previous literature. Multi-trait analyses revealed weak genetic correlations between PAP and BW, direct

and maternal WW, direct and maternal YW, and PWG of 0.19 ± 0.06, 0.23 ± 0.08, -0.05 ± 0.08, 0.13 ± 0.08, -0.01 ± 0.09, -0.11 ± 0.10, respectively. The results of this study suggest that selection for lower PAP score should have minimal influence on the growth performance of cattle at the CSU-BIC, which supports our hypothesis.

INTRODUCTION

A major risk for cattle raised in higher elevations is development of high altitude disease (HAD), commonly referred to as brisket disease. According to Enns et al. (2011), HAD falls within the class of diseases associated with non-transmittable environmental challenges, more directly related to adaptability. Prevalence of HAD in cattle has been reported to range from 0.4% to 40% in intermountain regions (Will et al., 1975; Salman et al., 1990).

High altitude disease is a consequence of pulmonary hypertension, which has a multifactorial pathophysiology, where not all contributing factors for the disease are fully understood (Humbert et al., 2004). Pulmonary hypertension is a disease of the small pulmonary arteries, characterized by narrowing of the pulmonary vasculature due to increased size of the arterial adventitia leading to a progressive increase in pulmonary vascular resistance, and consequently increasing right ventricle afterload with the potential to cause failure of the right ventricle (Humbert et al., 2004). Preventative measures typically focus on the identification and culling of high-risk individuals from the breeding program (Holt and Callan, 2007). Pulmonary arterial pressures (PAP) can be used as an indicator trait to confirm the presence of pulmonary hypertension due to high altitude (Holt and Callan, 2007) and is a moderately to highly heritable trait (0.20 to 0.46; Enns et al., 1992; Shirley et al., 2008; Cockrum et al., 2014). Therefore, it can be used to make selection decisions for genetic improvement. High altitude disease has been a

concern for the Colorado State University Beef Improvement Center (CSU-BIC) since the establishment of the ranch in 1950. Due to this concern, the CSU-BIC has used PAP as a selection tool in their breeding objective in an attempt to decrease the prevalence of the disease in the herd.

The objective of this research was to estimate heritabilities and determine the genetic relationships between PAP and performance traits including birth weight (BW), weaning weight (WW), yearling weight (YW), and post-weaning gain (PWG) through single-trait, 2-trait, and multi-trait analyses. Since the CSU-BIC has been selecting Angus cattle in a high elevation production system based on both weight performance and PAP scores, our hypothesis was that little to no genetic relationships exist between PAP and these performance traits. A better understanding of the relationship between PAP and performance traits would indicate what effect, if any, selection for PAP has on growth performance of cattle in the CSU-BIC.

MATERIALS AND METHODS

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

Cattle and PAP Scores. Data utilized in this study were queried from an existing database of performance trait measures of the CSU-BIC Angus herd. For this study, a state licensed veterinarian collected all PAP scores while cattle were restrained in a squeeze chute with a halter controlling the animal's head. Measurements of PAP were recorded in millimeters of mercury (mm Hg; Holt and Callan, 2007). A more detailed description of PAP collection procedure and scores are described by Holt and Callan (2007). Due to findings of other research showing that PAP at weaning and yearling were significantly different ($P < 0.05$) and should be treated as

different traits (Zeng et al., 2015). Pulmonary arterial pressure scores were restricted to those taken at yearling ages as outlined in Beef Improvement Federation (BIF) guidelines (http://beefimprovement.org/library-2/bif-guidelines). The average PAP age was 356 days, with a minimum 320 days and a maximum 410 days and a standard deviation of 19 days.

Since 1986, culling decisions at the CSU-BIC for replacement heifers and within-herd bulls have included PAP scores. Scores of ≤ 45 mm Hg were considered suitable for herd bulls and for replacement heifers, with the exception of a few females retained with higher PAP for research purposes. Outside AI sires, part of a PAP progeny-testing program for the beef industry, were not PAP tested; yet progeny from these sires were evaluated for their PAP and used in this study.

Environment and Cattle Management. The CSU-BIC was located near Saratoga, Wyoming along the North Platte River at an elevation of approximately 2,340 m. The ranch consisted of approximately 2,596 ha of land. There was 299 ha of irrigated hay meadows, 81 ha of irrigated alfalfa (pivot sprinkler), 348 ha of irrigated pasture with the remainder dry land, sagebrush rangeland, homestead and buildings. The annual average temperature in Saratoga was 7.3°C, the average high temperature was 28.3°C and the average low temperature was -9.4°C, with an annual precipitation of 30.5 millimeters including snowfall (MyForcast, 2015).

Yearling heifers were developed through grazing when forage was available but typically with alfalfa/grass hay supplementation in winter months, usually December to March. Target ADG for winter months was 0.5 kg/d. Yearling bulls were fed a high concentrate diet in a 120 d gain test, with an expected ADG of 1.5 kg/d. Pulmonary arterial pressure scores were collected on bulls at or near the end of the gain tests in March or April. Heifers were PAP tested at a similar time of the year.

Male calves were split into those that would enter the bull test and those that would become steers destined for the feedlot. Since steers were managed post-weaning at a different location and under different management and there were relatively few in comparison to bulls and heifers, they were omitted from the analyses on YW and PWG, as castration typically occurred at weaning. Therefore, subsequent statistical models included only bull and heifer effects.

Data. The data included performance records from 8,718 Angus cattle. Performance and PAP records from 1993 to 2014 were used and summarized in Tables 4.1 and 4.2. Table 4.1 includes the descriptive statistics of unadjusted phenotypic values for all traits: PAP, BW, WW, YW, and PWG. The WW and YW observations were also pre-adjusted for age based on BIF guidelines with descriptive statistics for age-adjusted weights were displayed in Table 4.2.

Separate analyses for pre-adjusted and unadjusted WW and YW dependent variables were implemented to evaluate the influence of standard (i.e. BIF) versus data-dependent (i.e. model) adjustments. Each analysis within the single-trait, two-trait, and multi-trait models was conducted using both sets of data with results presented in separate tables. Adjustments were based on BIF guidelines, where age-adjusted WW and YW was calculated as:

$$Adjusted\ WW\ = \frac{WW-BW}{Weaning\ Age} * 205\ +\ BW, \text{ and}$$

$$Adjusted\ YW\ = \frac{YW-WW}{Days\ between\ weights} * 160\ +\ adjusted\ WW,$$

respectively. In both age-adjusted WW and YW, age of dam was adjusted for through a fixed effect in the model. Using ANOVA, a coefficient of determination (R^2) was estimated to compare the use of age-adjusted WW/YW versus unadjusted WW/YW. Birth, weaning, and yearling weight values ≥ 5 standard deviations from the mean were eliminated.

Table 4.1. Descriptive statistics of unadjusted data available on pulmonary arterial pressure (PAP), birth weight (BW), unadjusted weaning weight (WW), unadjusted yearling weight (YW) and post-weaning gain (PWG) in the CSU-BIC[i] Angus herd.

Item	n	Minimum	Mean	Maximum	SD
PAP, mm Hg	5,776	21	42.4	139	9.9
BW, kg	8,695	12.2	36.2	56.7	5.1
WW, kg	8,010	58.5	213.5	368.3	31.8
YW, kg	5,580	166.9	345.6	584.2	83.8
PWG[ii], kg	5,453	1.0	121.9	382.9	63.7

[i] Colorado State University-Beef Improvement Center, Saratoga, Wyoming, elevation > 2,300 m
[ii] PWG = YW-WW/Days between weights*160

Table 4.2. Descriptive statistics of data available on pulmonary arterial pressure (PAP), birth weight (BW), age-adjusted[i] weaning weight (WW), age-adjusted[i] yearling weight (YW) and post-weaning gain (PWG) in the CSU-BIC[ii] Angus herd.

Item	n	Minimum	Mean	Maximum	SD
PAP, mm Hg	5,776	21	42.4	139	9.9
BW, kg	8,695	12.2	36.2	56.7	5.1
WW, kg	6,784	76.5	233.5	375.0	31.2
YW, kg	4,880	185.2	358.3	615.6	82.6
PWG[iii], kg	5,453	1.0	121.9	382.9	63.7

[i] Age-adjusted phenotypic observations, based on Beef Improvement Federation guidelines
[ii] Colorado State University-Beef Improvement Center, Saratoga, Wyoming, elevation > 2,300 m
[iii] PWG = YW - WW/Days between weights*160

At weaning, sex of the calves were defined as females (1) and males (2). At yearling, sex of the calves was separated into heifers (1) and bulls (2). Categories for age of dam were converted to BIF standard ages of 2, 3, 4, 5 to 9, 10, 11, 12, and 13+ (http://beefimprovement.org/library-2/bif-guidelines). The equation used to calculate post-weaning gain was:

$$PWG = \frac{YW - WW}{Days\ between\ weights} * 160.$$

Weaning age, yearling age, and PAP age were calculated by taking the difference between the date each trait was measured and birth date of the calf. Weaning weights were age-adjusted based on BIF guidelines. Weaning age averaged 190 d and ranged from 160 to 250 d, with a standard deviation of 17 d. Beef Improvement Federation recommends an age range for adjusted 365-d yearling weight to be 320 to 410 d. Therefore, yearling ages were truncated by these standards, resulting in an average age of 358 d and standard deviation of 24 d.

Weaning contemporary group (WCG) was a single fixed effect resulting from a combination of weaning date and year of birth. Yearling contemporary group (YCG) was a single fixed effect encompassing yearling date, weaning date, and year of birth. Yearling contemporary group effect was also fit for PWG and PAP. Any CG with only a single animal was eliminated.

Statistics. Heritability and genetic correlation estimates were executed using the software package ASReml 3.0 (Gilmour et al., 2009). The single-trait, two-trait, and multi-trait animal models were expressed as:

$$y_n = X_{(nxp)}b_{(px1)} + Z_{d_{(nxq)}}u_{d_{(qx1)}} + Z_{m_{(nxl)}}u_{m_{(lx1)}} + e,$$

where y represented the dependent variable(s) with n animal observations for each trait analyzed, X was an $n\ x\ p$ incidence matrix of p number of fixed effects, b was a vector of fixed effects, Z_d represented an $n\ x\ q$ incidence matrix of q number of direct (d) random effects, u_d was a vector of direct random effects, Z_m represented an $n\ x\ l$ incidence matrix of l number of maternal (m) random effects for weaning and yearling weight, u_m was a vector of maternal random effects, and e was vector of residual errors.

The (co)variance for the random effects for the two-trait analyses were expressed as follows:

$$V = \begin{bmatrix} d_1 \\ d_2 \\ m_1 \\ m_2 \\ p_1 \\ p_2 \\ e_1 \\ e_2 \end{bmatrix} = \begin{bmatrix} A\sigma_{d_1}^2 & A\sigma_{d_{12}} & A\sigma_{d_1m_1} & A\sigma_{d_1m_2} & 0 & 0 & 0 & 0 \\ A\sigma_{d_{21}} & A\sigma_{d_2}^2 & A\sigma_{d_2m_1} & A\sigma_{d_2m_2} & 0 & 0 & 0 & 0 \\ A\sigma_{d_1m_1} & A\sigma_{d_2m_1} & A\sigma_{m_1}^2 & A\sigma_{m_1m_2} & 0 & 0 & 0 & 0 \\ A\sigma_{d_1m_2} & A\sigma_{d_2m_2} & A\sigma_{m_2m_1} & A\sigma_{m_2}^2 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & I_{N_d}\sigma_{p_1}^2 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & I_{N_d}\sigma_{p_2}^2 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & I_N\sigma_{e_1}^2 & I_N\sigma_{e_{12}} \\ 0 & 0 & 0 & 0 & 0 & 0 & I_N\sigma_{e_{21}} & I_N\sigma_{e_2}^2 \end{bmatrix},$$

where A was Wright's numerator relationship matrix, $\sigma_{d_1}^2$ was the direct genetic variance the first trait, $\sigma_{d_2}^2$ was the direct genetic variance the second trait, $\sigma_{m_1}^2$ was the maternal genetic variance for the first trait, $\sigma_{m_2}^2$ was the maternal genetic variance for the second trait, $\sigma_{d_{12}}$ was the direct genetic covariance between the first and second trait, $\sigma_{d_1m_1}$ was the covariance between the direct component of the first trait and the maternal component of the first trait, $\sigma_{d_2m_1}$ was the covariance between the direct component of the second trait and the maternal component of the first trait, I was an identity matrix, N_d was the number of dams and N was the number of animals, $\sigma_{p_1}^2$ was the permanent maternal environmental variance for the first trait, $\sigma_{p_2}^2$ was the permanent maternal environmental variance for the second trait, $\sigma_{e_1}^2$ was residual variance for the first trait, $\sigma_{e_2}^2$ was residual variance for the second trait, and $\sigma_{e_{12}}$ was residual covariance between the first and second traits. It was also assumed that the genetic and residual effects followed a multi-variate normal distribution with zero covariance between genetic and residual effects. Given that maternal and permanent environmental effects were only used with WW and YW, lines 3 to 6 of the (co)variance structure were only used when WW and (or) YW were used as dependent variables.

The (co)variance for the random effects for the multi-trait analyses were expressed as follows:

$$V = \begin{bmatrix} d_1 \\ d_2 \\ d_3 \\ d_4 \\ m_1 \\ m_2 \\ p_1 \\ p_2 \\ e_1 \\ e_2 \\ e_3 \\ e_4 \end{bmatrix} =$$

$$\begin{bmatrix} A\sigma_{d_1}^2 & A\sigma_{d_{12}} & A\sigma_{d_{13}} & A\sigma_{d_{14}} & A\sigma_{d_1m_1} & A\sigma_{d_1m_2} & 0 & 0 & 0 & 0 & 0 & 0 \\ A\sigma_{d_{12}} & A\sigma_{d_2}^2 & A\sigma_{d_{23}} & A\sigma_{d_{24}} & A\sigma_{d_2m_1} & A\sigma_{d_2m_2} & 0 & 0 & 0 & 0 & 0 & 0 \\ A\sigma_{d_{12}} & A\sigma_{d_{12}} & A\sigma_{d_3}^2 & A\sigma_{d_{34}} & A\sigma_{d_3m_1} & A\sigma_{d_3m_2} & 0 & 0 & 0 & 0 & 0 & 0 \\ A\sigma_{d_{12}} & A\sigma_{d_{12}} & A\sigma_{d_{12}} & A\sigma_{d_4}^2 & A\sigma_{d_4m_1} & A\sigma_{d_4m_2} & 0 & 0 & 0 & 0 & 0 & 0 \\ A\sigma_{d_1m_1} & A\sigma_{d_2m_1} & A\sigma_{d_3m_1} & A\sigma_{d_4m_1} & A\sigma_{m_1}^2 & A\sigma_{m_1m_2} & 0 & 0 & 0 & 0 & 0 & 0 \\ A\sigma_{d_1m_2} & A\sigma_{d_2m_2} & A\sigma_{d_3m_2} & A\sigma_{d_4m_2} & A\sigma_{m_2m_1} & A\sigma_{m_2}^2 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & I_{N_d}\sigma_{p_1}^2 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & I_{N_d}\sigma_{p_2}^2 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & I_N\sigma_{e_1}^2 & I_N\sigma_{e_{11}} & I_N\sigma_{e_{13}} & I_N\sigma_{e_{14}} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & I_N\sigma_{e_{21}} & I_N\sigma_{e_2}^2 & I_N\sigma_{e_{23}} & I_N\sigma_{e_{24}} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & I_N\sigma_{e_{31}} & I_N\sigma_{e_{32}} & I_N\sigma_{e_3}^2 & I_N\sigma_{e_{34}} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & I_N\sigma_{e_{41}} & I_N\sigma_{e_{42}} & I_N\sigma_{e_{43}} & I_N\sigma_{e_4}^2 \end{bmatrix},$$

where A was Wright's numerator relationship matrix, $\sigma_{d_1}^2$ was the direct genetic variance the first trait, $\sigma_{d_2}^2$ for the second trait (etc. for the third and fourth traits), $\sigma_{m_1}^2$ was the maternal genetic variance for the first trait, $\sigma_{m_2}^2$ was the maternal genetic variance for the second trait, $\sigma_{d_{12}}$ was the direct genetic covariance between the first and second trait (etc. for all combinations of the four traits), $\sigma_{d_1m_1}$ was the covariance between the direct component of the first trait and the maternal component of the first trait (etc. for all combinations of direct and maternal traits), I was an identity matrix, N_d was the number of dams and N was the number of animals, $\sigma_{p_1}^2$ was the permanent maternal environmental variance for the first trait, $\sigma_{p_2}^2$ was the permanent maternal environmental variance for the second trait, $\sigma_{e_1}^2$ was residual variance for the

first trait (etc. for the second, third, and fourth traits), and $\sigma_{e_{12}}$ was residual covariance between the first and second traits (etc. for all combinations of the four traits). It was also assumed that the genetic and residual effects followed a multi-variate normal distribution with zero covariance between genetic and residual effects. Given that maternal and permanent environmental effects were only used with dependent variables WW and YW, lines 5 to 8 of the (co)variance structure were only used when WW and (or) YW was used as dependent variables.

The fixed effects to be used in the single-trait models included: year of birth, weaning sex, and age of dam for BW. Sex, age of the dam, age of the animal at time when phenotypic observation was measured, and WCG or YCG were used as fixed effects for WW and YW. The only differentiation between these analyses would be the use of WCG for WW and YCG for YW. The fixed effects used for PWG included yearling sex, age of the dam, and YCG. The fixed effects used for PAP included yearling sex, age, date and YCG. The random effects to be used in the single-trait models included: additive direct for all traits, with additive maternal and permanent environmental effects for WW and (or) YW only.

Wald F statistics were utilized to test the significance of the fixed effects used in the analyses. All fixed effects, except age of dam and yearling age, in each of the single-trait models were significant ($P < 0.001$). Age of dam was significant ($P < 0.001$) for BW, WW, and YW dependent variables. However, age of dam for neither PWG nor PAP dependent variables was significant ($P > 0.05$), and was subsequently removed from the model in all further analyses of those traits. Weaning age and PAP age were significant ($P < 0.001$) effects for the single-trait analyses on the dependent variables WW and PAP, respectively. Yearling age was significant on the dependent variable unadjusted YW ($P < 0.001$). In order to not double count for the effect of age on weight, weaning age and yearling age were not used in the age-adjusted WW and YW

analyses. All of the same fixed and random effects used in the single-trait analyses were also used in the subsequent two-trait and multi-trait analyses (Table 4.3).

Table 4.3. Fixed and random effects included in the single-trait, two-trait, and multi-trait animal models analyzed for each trait (phenotypic observation) in CSU-BIC[i] Angus herd data (n = 8,718).

	Model				
Effect	Birth Weight	Weaning Weight	Yearling Weight	Post-Weaning Gain	PAP[ii]
Fixed					
Year of Birth	✓				
Sex[iii]	✓	✓	✓ [viii]	✓ [viii]	✓ [viii]
Age of Dam	✓	✓	✓		
Age[iv]		✓	✓		✓
Date[v]					
WCG[vi]		✓			
YCG[vii]			✓	✓	✓
Random					
Direct additive	✓	✓	✓	✓	✓
Maternal additive		✓	✓		
Permanent Environment		✓	✓		

[i] Colorado State University-Beef Improvement Center, Saratoga, Wyoming, elevation > 2,300 m
[ii] Pulmonary arterial pressure
[iii] Females (1) and Males (2)
[iv] Age of animals when phenotypic observation was taken/measured on the animals
[v] Date when phenotypic observation was taken/measured on the animals
[vi] Weaning Contemporary Group = weaning date_year of birth
[vii] Yearling Contemporary Group = yearling date_weaning date_year of birth
[viii] Yearling sex separated into heifers (1) and bulls (2). Heifers and bulls only used due to management

The single-trait analyses included an examination of PAP, BW, age-adjusted and unadjusted WW, age-adjusted and unadjusted YW, and PWG, individually. Both direct and maternal random effects were fit in all analyses using WW and YW, the singe-trait analyses were

conducted to obtain heritability estimates and starting values applicable for use in the two-trait analyses.

The two-trait analyses were conducted with PAP and each of the weight performance traits. Two-trait analyses were also conducted between each of the weight traits to obtain correlations amongst the traits. The two-trait analyses yielded heritability estimates for each trait, genetic and residual variances, and starting values applicable to use in the multi-trait analyses.

Two of the four multi-trait analyses were conducted with PAP, BW, age-adjusted or unadjusted WW, and age-adjusted or unadjusted YW, simultaneously to obtain heritabilities and genetic correlations. Both direct and maternal random effects were fit for WW and YW in the analysis. A likelihood ratio test was conducted to determine if having a maternal YW random effect was statistically significant. The other two of the four multi-trait analyses were conducted with PAP, BW, age-adjusted or unadjusted WW, and PWG, simultaneously. Both direct and maternal random effects were fit for WW only. Yearling weight and PWG weight traits were not executed in the same evaluation because of the high genetic correlation between two as a result of the part-whole relationship.

RESULTS AND DISCUSSION

Single-Trait Analyses. The heritability estimate for PAP was 0.23 ± 0.03, falling within the range of previous reports (0.20 to 0.46; Enns et al., 1992; Shirley et al., 2008; Cockrum et al., 2014). Estimates for all other traits in the single-trait analyses can be found in Tables 4.4 and 4.5. Table 4.4 utilized unadjusted phenotypic observations for WW and YW. Table 4.5 utilized age-adjusted phenotypic observations for WW and YW based on BIF guidelines. From the ANOVA, adjusted R^2 for using unadjusted WW observation was 0.33, whereas the adjusted R^2 for using an

adjusted WW observation was 0.17. The coefficient of determination illustrates that our model fixed effects explained more of the variation with unadjusted WW than with age-adjusted WW. Adjusted R^2 for using a unadjusted YW observation was 0.67, whereas the adjusted R^2 for using an age-adjusted YW observation was 0.48. The coefficient of determination illustrates that our model fixed effects explained more of the variation with unadjusted YW than with age-adjusted YW.

The heritability estimate for BW (0.58 ± 0.03) was significantly higher than the average BW heritability (0.40) from previous reports (Meyer, 1992b; Shirley et al., 2008) with the exception being the estimate of Mackinnon et al. (1991), where the heritability was estimated as 0.61. However, that estimate was for Zebu-cross cattle and not Angus as in the current study. In a spring 2015 Angus National Cattle Evaluation, the American Angus Association reported a heritability estimate for BW of 0.44 (American Angus Association, 2015). The potential explanation for the high BW heritability could be due to focused and intensive selection for decreased BW and increased calving ease in the CSU-BIC herd.

Heritability estimates for unadjusted WW direct and maternal were 0.16 ± 0.03 and 0.16 ± 0.04, respectively. These estimates were both reasonable and in range of previously reported estimate of 0.12 to 0.26 for direct and 0.12 to 0.28 for maternal in Angus cattle (Waldron et al., 1993; Williams et al., 2012). The genetic correlation between direct and maternal unadjusted WW (-0.31 ± 0.15) was reasonable compared to an estimate of direct-maternal WW component of -0.34 described by Williams et al. (2012).

Likewise, the unadjusted YW direct heritability estimate (0.24 ± 0.06) obtained was lower then the typical heritability of previous research findings (0.25 to 0.34; Mackinnon et al., 1991; Robinson, 1996). Although it is a sensible estimate, the lower heritability may be due to

the addition of random maternal effect to the analysis. Meyer (1992b) mentioned that the environmental covariance between dam and offspring is expected to bias the estimate of the direct-maternal genetic correlation downwards; thus, decreasing phenotypic variance and increasing heritability estimates. The maternal YW heritability (0.19 ± 0.06) was included in the model to account for any residual genetic effects of the dam from the pre- and post-weaning growth period. Of the reports that have examined the maternal effect on YW, our estimates were within the range of estimates previously reported (0.13 to 0.20; Mackinnon et al., 1991; Robinson, 1996). The correlation between direct and maternal unadjusted YW was estimated to be -0.48 ± 0.14. Previous reports described varying results for this correlation ranging from 0.49 to -0.73 (Meyer, 1992b; Robinson, 1996). The degree of variation in the estimates could be due to pedigree and (or) data structure differences of those reports. Possible reasons for the large, negative estimates for direct-maternal correlations are the pedigree relationships, experimental design, size of the data, or bias due to some missing component (Meyer, 1992a). Post-weaning gain heritability (0.14 ± 0.03) was an estimate that also fell outside the range of previously reported heritability estimates of 0.19 to 0.26 (Williams et al., 2012; Berge et al., 2014). However, as PWG is a reflection of both WW and YW, the heritability appeared to be lower than expected given the heritabilities of WW and YW. At closer examination, the heritability for PWG was separated by sex (heifers, bulls, steers). When this occurred, the heritability estimate of PWG for heifers was 0.22 ± 0.04, bulls was 0.11 ± 0.06, and steers was 0.00 ± 0.13. This shows that the heritability for PWG of heifers and bulls was influenced by the low heritability for PWG of the males.

Table 4.4. Single-trait model heritabilities for each trait & genetic correlations ± SE between direct and maternal traits using unadjusted weaning and yearling weights.

Trait	Heritability ± SE	Genetic Correlations
Pulmonary Arterial Pressure	0.23 ± 0.03	-
Birth Weight	0.58 ± 0.03	-
Weaning Weight $_{d}$[i]	0.16 ± 0.03	-0.31 ± 0.15
Weaning Weight $_{m}$[ii]	0.16 ± 0.04	
Yearling Weight $_{d}$	0.24 ± 0.06	-0.48 ± 0.14
Yearling Weight $_{m}$	0.19 ± 0.06	
Post-Weaning Gain	0.14 ± 0.03	-

[i] Additive direct
[ii] Additive maternal

The single-trait analyses conducted with age-adjusted WW and YW yielded heritability estimates for WW direct and maternal as 0.14 ± 0.03 and 0.16 ± 0.04 respectively. These estimates were both reasonable and in range of previously reported estimates of 0.07 to 0.19 for direct and 0.08 to 0.18 for maternal for Angus cattle (Meyer, 1992b; Koots et al., 1994; Shirley et al., 2008; Williams et al., 2012). The genetic correlation between direct and maternal age-adjusted WW (-0.44 ± 0.17) was reasonable compared to other estimates of direct-maternal WW components of -0.34 to -0.44 (Shirley et al., 2008; Williams et al., 2012).

The age-adjusted YW direct heritability estimate (0.22 ± 0.06) was lower than the average heritability of previous research findings (0.25 to 0.34; Mackinnon et al., 1991; Robinson, 1996). Although it is a sensible estimate, the lower heritability may be due to the addition of random maternal effect to the analysis. Meyer (1992b) showed through differing model comparisons that the direct heritability could be reduced due to the estimation of maternal heritability. Of the reports that have examined maternal effect in yearling weight, our estimate of 0.16 ± 0.06 falls within the range of estimates previously reported (0.04 to 0.20), as it also did with unadjusted YW (Mackinnon et al., 1991; Meyer, 1992b).

Table 4.5. Single-trait model heritabilities for each trait & genetic correlations ± SE between direct and maternal components using age-adjusted[i] weaning and yearling weights.

Trait	Heritability ± SE	Genetic Correlations
Pulmonary Arterial Pressure	0.23 ± 0.03	-
Birth Weight	0.58 ± 0.03	-
Weaning Weight[i] $_{d}$[ii]	0.14 ± 0.03	-0.27 ± 0.17
Weaning Weight[i] $_{m}$[iii]	0.16 ± 0.04	
Yearling Weight[i] $_{d}$	0.22 ± 0.06	-0.44 ± 0.17
Yearling Weight[i] $_{m}$	0.16 ± 0.06	
Post-Weaning Gain	0.14 ± 0.03	-

[i] Age-adjusted phenotypic observations based on Beef Improvement Federation guidelines
[ii] Additive direct
[iii] Additive maternal

Two-trait Analyses. The two-trait analyses were conducted with both unadjusted and age-adjusted weaning and yearling weights and results were presented in Table 4.6 and 4.7, respectively.

Unadjusted WW & YW. Table 4.6 presents the results of the each of the two-trait analyses conducted using unadjusted phenotypic observations for WW and YW. Above the diagonal in Table 4.6 were the genetic correlations of all of the traits evaluated. The first row of the table represented the genetic correlations between PAP and each weight trait. The correlations were low, ranging from -0.10 to 0.19. From this, it appears that a weak relationship exists between PAP scores and weight traits at birth, weaning, yearling, and PWG. All other genetic correlations calculated between weights traits appeared to be logical and reasonably close to those calculated in previous research.

On the diagonal of Table 4.6, were heritabilities and their standard errors for each of the traits in the analysis. Given that each trait was analyzed multiple times in the two-trait analyses, the heritability estimates were averages of those traits across all analyses. We expected to have

similar heritability estimates in the two-trait analysis as those in the single-trait analyses. Heritability estimates for traits PAP, BW, and PWG were within 0.03 units from those found in the single-trait analyses. However, the direct and maternal WW, and direct and maternal YW heritability estimates all increased considerably. These increases in the estimates were likely due to the use of two-trait models, where single-trait analyses allowed for the exclusion of animals without observations for a particular trait; however, two-trait models require the inclusion of animals with missing observations of one trait in order to include observations on another trait or elimination of observations on animals with only partial data.

The genetic correlations between direct and maternal components of WW and of YW decreased from those found in the single-trait analyses. Negative correlations were expected between direct and maternal effects as a consequence of natural selection for an intermediate optima (Garrick et al., 1989). Maniatis and Pollott (2003) reported moderate to high, negative genetic correlations, ranging from -0.46 to -0.99, between direct and maternal early weight traits in cattle. The results of Maniatis and Pollott (2003) provided strong evidence that parameter estimates are influenced by the number of progeny per dam, as well as the proportion of dams with recorded performance (Maniatis and Pollott, 2003). In their study, the experimental data structure consisted of 10% records on dams and is thought to have influenced the large negative correlations they received. However, the data used in this analysis has an average of 2.4 progeny per dam and over 90% of dams have their own records. Therefore, we do not believe that data structure is influencing our outcome of a negative genetic correlation.

There was a decrease in the genetic covariance between direct and maternal components and increases in both the genetic and residual variances; thus, our heritability estimates for direct WW and direct YW increased from what was found in the single-trait analyses. There was no

conclusive evidence on what the genetic relationship between direct and maternal components of YW should be, as previous studies range from strongly, negative -0.72 (Baker, 1980) to moderately, positive 0.33 (Meyer, 1992b).

Table 4.6. Heritabilities[i] (**diagonal**) and genetic correlations (above diagonal) ± SE from each of the two-trait models of pulmonary arterial pressure (PAP), birth weight (BW), unadjusted weaning weight (WW; direct and maternal), unadjusted yearling weight (YW; direct and maternal), and post-weaning gain (PWG) phenotypic observations (n = 8,718).

Trait	PAP	BW	WW_d[ii]	WW_m[iii]	YW_d	YW_m	PWG
PAP	**0.26 ± 0.03**	0.18 ± 0.06	0.19 ± 0.10	0.01 ± 0.10	0.08 ± 0.09	0.05 ± 0.10	-0.10 ± 0.10
BW		**0.58 ± 0.02**	0.49 ± 0.05	-0.17 ± 0.07	0.37 ± 0.05	-0.12 ± 0.07	0.27 ± 0.07
WW_d			**0.33 ± 0.04**	-0.52 ± 0.07	0.93 ± 0.02	-0.66 ± 0.05	0.23 ± 0.11
WW_m				**0.21 ± 0.03**	-0.44 ± 0.06	0.96 ± 0.02	-0.12 ± 0.11
YW_d					**0.45 ± 0.05**	-0.64 ± 0.05	0.63 ± 0.06
YW_m						**0.17 ± 0.03**	-0.16 ± 0.11
PWG							**0.13 ± 0.02**

[i] Average heritabilities for each trait, given the total number of analyses run with that trait
[ii] Additive direct
[iii] Additive maternal

Age-adjusted WW & YW. Table 4.7 presents the heritabilities and genetic correlations using age-adjusted WW and YW dependent variables. The first row of Table 4.7 represented the genetic correlations between PAP and each weight trait. Similar to the results in Table 4.6, the correlations were low, ranging from -0.10 to 0.18. Again, from these results, it appears that a weak relationship exists between PAP scores and weight traits at birth, weaning, yearling, and PWG. All other genetic correlations calculated between weight traits appeared to be logical and reasonably close to those calculated in previous research (Koots et al., 1994; Bennett and Gregory, 1996).

The heritability estimates on the diagonal of Table 4.7 more closely resembled those from the single-trait analyses utilizing age-adjusted WW and YW. All heritability estimates were within 0.06 units from those found in the single-trait analyses. The correlation between direct

and maternal components for WW was similar to the single-trait analysis, whereas the correlation between direct and maternal components of YW increased from -0.44 to -0.29. Again, negative correlations were expected between direct and maternal effects (Garrick et al., 1989). To our knowledge, this is the first estimate of the genetic relationship between PAP and maternal effects on yearling weight.

Table 4.7. Heritabilities[i] (**diagonal**) and genetic correlations (above diagonal) ± SE from each of the two-trait models of pulmonary arterial pressure (PAP), birth weight (BW), age-adjusted[ii] weaning weight (WW; direct and maternal), age-adjusted[ii] yearling weight (YW; direct and maternal), and post-weaning gain (PWG) phenotypic observations (n = 8,718).

Trait	PAP	BW	WW_d[iii]	WW_m[iv]	YW_d	YW_m	PWG
PAP	**0.26 ± 0.03**	0.18 ± 0.06	0.13 ± 0.12	0.08 ± 0.11	0.00 ± 0.12	0.13 ± 0.15	-0.10 ± 0.10
BW		**0.58 ± 0.02**	0.71 ± 0.05	-0.21 ± 0.08	0.66 ± 0.06	-0.21 ± 0.12	0.27 ± 0.07
WW_d			**0.18 ± 0.03**	-0.30 ± 0.11	0.89 ± 0.04	-0.28 ± 0.12	0.19 ± 0.14
WW_m				**0.19 ± 0.04**	-0.05 ± 0.12	0.97 ± 0.02	-0.09 ± 0.12
YW_d					**0.23 ± 0.04**	-0.29 ± 0.13	0.79 ± 0.06
YW_m						**0.10 ± 0.03**	-0.16 ± 0.13
PWG							**0.13 ± 0.02**

[i] Average heritabilities for each trait, given the total number of analyses run with that trait
[ii] Age adjusted phenotypic observation, based on Beef Improvement Federation guidelines
[iii] Additive direct
[iv] Additive maternal

Multi-trait Analyses. A multi-trait analysis produces genetic correlations between all traits in the model. Since an objective of this study was to determine the relationships between PAP and each performance trait in Angus cattle, the additional correlations were not necessary to make conclusions for this paper, but provide an overview of these genetic relationships and lend further evidence for the appropriate use of the data to estimate the genetic relationships with PAP. Four total multi-trait analyses were conducted. Two analyses examined PAP, BW, direct and maternal components of WW, and direct and maternal components of YW. The differentiation between the two being the use of unadjusted WW and YW versus age-adjusted

WW and YW phenotypic observations. The other two analyses examined PAP, BW, direct and maternal WW, and PWG. Again, the difference between the 2 analyses was the use of unadjusted and age-adjusted WW phenotypic observations.

Yearling Weight. Table 4.8 and 4.9 display the results of two multi-trait analyses of PAP, BW, direct and maternal WW, and direct and maternal YW. Table 4.8 includes unadjusted WW and YW phenotypic observations, while Table 4.9 utilizes age-adjusted WW and YW. We expected to receive heritability estimates and genetic correlations similar to those calculated in the two-trait analyses. In both the unadjusted and age-adjusted analyses, heritability estimates for PAP (0.26 ± 0.03) and BW (0.58 ± 0.02) were approximately the same as those reported for the two-trait analyses.

In the analysis of unadjusted data, the heritability estimates for direct and maternal WW and YW increased relative to those reported in the two-trait analyses. The increase in the heritability may have been due to the use of a multi-trait model. These models have the ability to increase heritability estimates due factors including: the increase in number of traits used and information available, and the consideration of the (co)variance structures amongst those traits (Thompson and Meyer, 1986).

Correlations of PAP and maternal WW and PAP and maternal YW were -0.05 ± 0.08 and -0.01 ± 0.09, respectively. The estimates, given their standard errors, include zero, and therefore it can be inferred that no correlation exists between the traits. Weak relationships exist between the remaining traits PAP and BW, WW direct, and YW direct. In opposition to the results in our multi-trait analyses, Shirley et al. (2008) estimated moderate to strong correlations between PAP and BW (0.49 ± 0.12) and PAP and WW direct (0.51 ± 0.02). This difference may be explained through the differing herds and management of the Angus cattle evaluated in the two studies.

Shirley et al. (2008) did have similar results with regards to the genetic correlation between PAP and WW maternal (-0.05 ± 0.14). The only other correlation between PAP and YW came from Schimmel (1981). He found a highly negative correlation between PAP and YW (-0.75 ± 0.65) with bulls from multiple sire lines. Due to the lack of computer power and capabilities in 1981, the correlation estimate from Schimmel may not be as credible when compared to the current research findings.

The genetic correlation between unadjusted WW direct and maternal decreased from -0.52 to -0.67. The genetic correlation between unadjusted YW direct and maternal stayed the same at -0.64. All other genetic correlations were similar to those estimated in the two-trait analyses.

Table 4.8. Heritabilities (**diagonal**) and genetic correlations (above diagonal) ± SE from the multi-trait model for pulmonary arterial pressure (PAP), birth weight (BW), unadjusted weaning weight (WW; direct and maternal), and unadjusted yearling weight (YW; direct and maternal) in CSU-BIC[i] herd (n = 8,718).

Trait	PAP	BW	WW_d[ii]	WW_m[iii]	YW_d	YW_m
PAP	**0.25 ± 0.03**	0.19 ± 0.06	0.23 ± 0.08	-0.05 ± 0.08	0.13 ± 0.08	-0.01 ± 0.09
BW		**0.58 ± 0.02**	0.38 ± 0.05	-0.12 ± 0.05	0.34 ± 0.05	-0.07 ± 0.06
WW_d			**0.41 ± 0.04**	-0.67 ± 0.05	0.93 ± 0.02	-0.46 ± 0.06
WW_m				**0.28 ± 0.03**	-0.53 ± 0.05	0.96 ± 0.02
YW_d					**0.48 ± 0.04**	-0.64 ± 0.05
YW_m						**0.23 ± 0.02**

[i] Colorado State University-Beef Improvement Center, Saratoga, Wyoming, elevation > 2,300 m

[ii] Additive direct

[iii] Additive maternal

The analysis of age-adjusted WW and YW was presented in Table 4.9. The heritability estimates for direct and maternal WW and YW appeared larger from the two-trait analysis heritabilities. As stated previously, the increase in the heritability may be due to the use of a

multi-trait model. Multi-trait analyses have the ability to reduce prediction error variance (PEV) and improve accuracy of evaluations, as well as remove bias caused by selection (Schaeffer, 1984; Thompson and Meyer, 1986). The correlations between the direct and maternal components of both age-adjusted WW and YW are larger then the estimates in the two-trait analyses. This reiterates that a reduction in the error variance through the use of a multi-trait model can cause an increase in our heritabilities.

The genetic correlations between PAP and weight traits BW, WW, and YW appeared similar to those found in the age-adjusted two-trait analysis ranging from 0.02 to 0.17. Correlations of PAP and age-adjusted maternal WW, age-adjusted direct YW, and age-adjusted maternal YW were 0.02 ± 0.09, 0.08 ± 0.10, 0.04 ± 0.10, respectively. The estimates, given their standard errors, include zero, and therefore it can be inferred that no correlation exists between these traits. Only weak relationships between PAP and BW and PAP and WW direct exist for the age-adjusted phenotypes.

Table 4.9. Heritability estimates (**diagonal**) and genetic correlations (above diagonal) ± SE from the multi-trait model for pulmonary arterial pressure (PAP), birth weight (BW), age-adjusted[i] weaning weight (WW; direct and maternal), and age-adjusted[i] yearling weight (YW; direct and maternal) in CSU-BIC[ii] herd (n = 8,718).

Trait	PAP	BW	WW_d[iii]	WW_m[iv]	YW_d	YW_m
PAP	**0.26 ± 0.03**	0.18 ± 0.06	0.17 ± 0.10	0.02 ± 0.09	0.08 ± 0.10	0.04 ± 0.10
BW		**0.58 ± 0.02**	0.71 ± 0.05	-0.15 ± 0.06	0.67 ± 0.05	-0.13 ± 0.07
WW_d			**0.21 ± 0.03**	-0.23 ± 0.10	0.92 ± 0.03	-0.25 ± 0.11
WW_m				**0.25 ± 0.03**	-0.11 ± 0.10	0.96 ± 0.02
YW_d					**0.27 ± 0.04**	-0.20 ± 0.10
YW_m						**0.16 ± 0.02**

[i] Age-adjusted phenotypic observations, based on Beef Improvement Federation guidelines
[ii] Colorado State University-Beef Improvement Center, Saratoga, Wyoming, elevation > 2,300 m
[iii] Additive direct
[iv] Additive maternal

Post-Weaning Gain. Tables 4.10 and 4.11 represented the results of the other two multi-trait analyses conducted with PAP, BW, direct and maternal WW, and PWG. They were differentiated from one another through the use of age-adjusted and unadjusted WW as a dependent variable. As stated previously, YW was excluded from these multi-trait analyses due to a part-whole relationship that exists between YW and PWG, which introduced convergence problems. Table 4.10 utilizes unadjusted WW, while Table 4.11 utilizes age-adjusted WW.

In Table 4.10, heritability estimates for PAP, BW, unadjusted direct and maternal WW, and PWG appeared reasonable given estimates reported in previous literature (Meyer, 1992b; Robinson, 1996; Berge et al., 2014). Most noteworthy in this analysis were the weak correlations between PAP and all of the weight traits. The highest genetic correlations were 0.19 ± 0.06 and 0.24 ± 0.09 for PAP with BW and PAP with direct WW, respectively. The genetic correlation between PAP and maternal WW (-0.04 ± 0.10), given its standard error includes zero. Thus far, no research other than the current work has examined the correlation between PAP and PWG.

Table 4.10. Heritability estimates (**diagonal**) and genetic correlations (above diagonal) ± SE from the multi-trait model for pulmonary arterial pressure (PAP), birth weight (BW), unadjusted weaning weight (WW; direct and maternal), and post-weaning gain (PWG) in CSU-BIC[i] herd (n = 8,718).

Trait	PAP	BW	WW_d[iii]	WW_m[iv]	PWG
PAP	**0.26 ± 0.03**	0.19 ± 0.06	0.24 ± 0.09	-0.04 ± 0.10	-0.11 ± 0.10
BW		**0.58 ± 0.02**	0.50 ± 0.05	-0.16 ± 0.07	0.28 ± 0.07
WW_d			**0.30 ± 0.03**	-0.53 ± 0.07	0.31 ± 0.10
WW_m				**0.16 ± 0.03**	-0.22 ± 0.11
PWG					**0.12 ± 0.02**

[i] Colorado State University-Beef Improvement Center, Saratoga, Wyoming, elevation > 2,300 m
[ii] Additive direct
[iii] Additive maternal

Table 4.11 represented the results of the multi-trait analysis utilizing WW age-adjusted based on BIF guidelines. All heritability estimates appeared to be reasonable and similar to estimates of previous research, as well as estimates in the two-trait analyses (Meyer, 1992b; Robinson, 1996; Williams et al., 2012; Berge et al., 2014). Similar to the results of Table 4.10, the genetic correlations between PAP and the weight traits were weak or non-existent ranging from -0.09 to 0.18. The correlation between PAP and maternal WW (0.03 ± 0.11), and PAP and PWG (-0.09 ± 0.10), given its standard errors include zero and it can be inferred that not relationship exists between these traits.

Table 4.11. Heritability estimates (**diagonal**) and genetic correlations (above diagonal) ± SE from the multi-trait model for pulmonary arterial pressure (PAP), birth weight (BW), age-adjusted[i] weaning weight (WW; direct and maternal), and post-weaning gain (PWG) in CSU-BIC[ii] herd (n = 8,718).

Trait	PAP	BW	WW_d[iii]	WW_m[iv]	PWG
PAP	**0.26 ± 0.03**	0.18 ± 0.06	0.18 ± 0.10	0.03 ± 0.11	-0.09 ± 0.10
BW		**0.58 ± 0.02**	0.72 ± 0.05	-0.20 ± 0.08	0.27 ± 0.07
WW_d			**0.21 ± 0.03**	-0.33 ± 0.11	0.31 ± 0.11
WW_m				**0.13 ± 0.03**	-0.23 ± 0.12
PWG					**0.12 ± 0.03**

[i] Age-adjusted phenotypic observations, based on Beef Improvement Federation guidelines
[ii] Colorado State University-Beef Improvement Center, Saratoga, Wyoming, elevation > 2,300 m
[iii] Additive direct
[iv] Additive maternal

CONCLUSIONS

From the results of correlations from the two-trait and multi-trait analyses, we accept our hypothesis and conclude there were only weak genetic relationships between PAP and the weight traits at birth, weaning, yearling and PWG in the CSU-BIC Angus herd. The genetic relationship

between PAP scores and other performance traits appeared minimal. As well, there does not appear to be a substantial difference in estimates of heritability and genetic correlations in the use of unadjusted verse age-adjusted WW or YW dependent variables.

IMPLICATIONS

Results suggest that genetic selection to help reduce incidence of pulmonary hypertension through lower PAP values can occur without adversely affecting growth performance in cattle at the CSU-BIC. As well, the results were contradictory to a report by Shirley et al. (2008) using data from another Angus seedstock herd in mountainous Colorado. The results of this study can be communicated to producers in similar environments, where selection for high altitude adaptability is paramount, yet, where selection to improve performance can help overall operation profitability.

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