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Inheritance of pulmonary arterial pressure in Angus cattle and its correlation with growth¹

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ABSTRACT: Pulmonary arterial pressure (PAP) is an indicator of resistance to blood flow through the lungs and when measured at high altitude is a reliable predictor of susceptibility of an animal to brisket disease, a noninfectious cardiac pulmonary condition. (Co)-variance components for PAP, birth weight, and adjusted 205-d weaning weight were estimated from 2,305 spring-born, registered Angus cattle from a Colorado ranch at an elevation of 1,981 m. A single measure of PAP was collected after weaning on animals born from 1984 to 2003. The same licensed veterinarian measured every animal. Multitrait animal models with and without PAP maternal effects were fitted for a pedigree including 132 sires and 793 dams. The interaction of year \times sex was a significant fixed effect ($P < 0.05$) for PAP, but age of dam was not. Age at PAP testing was a significant ($P < 0.1$) linear covariate for PAP, and scores increased 0.012 ± 0.007 mmHg·d⁻¹ of age. Heritability of PAP direct was 0.34 ± 0.05 . Maternal heritability converged to a boundary at 0.0, and the model with

maternal genetic effects for PAP was not significantly better than a model with only direct effects. Phenotypically, PAP was uncorrelated with birth or weaning weights. Genetically, PAP appeared to have positive, unfavorable relationships with direct effects for birth (0.49 ± 0.12) and weaning weight (0.50 ± 0.18). Positive correlations imply sires whose offspring exhibited resistance to brisket disease had lower weights and gains. A model that evaluated PAP in females and males as different traits had heritability estimates for each sex of 0.38 ± 0.07 and 0.46 ± 0.09 , respectively, with a genetic correlation of 0.64 ± 0.12 between the sexes and was not significantly better than the model assuming homogeneity by sex and a unit genetic correlation between sexes. The results suggest that PAP is moderately heritable in spring-born Angus cattle acclimatized and tested at high altitude, and selection for low PAP scores would be effective. Selection for growth at low altitude will produce cattle less suited to high altitude.

Key words: cattle, growth, heritability, maternal effect, pulmonary arterial pressure

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INTRODUCTION

High altitude or brisket disease is characterized by right ventricular hypertrophy and edema of the chest and brisket in domestic cattle at altitudes above 1,500 m. The incidence and severity of the disease increase with altitude and ultimately lead to death (Puntriano,

1954; Alexander and Jensen, 1959). First reported in 1915 (Glover and Newsom, 1915), this noninfectious cardiopulmonary condition occurs in 0.5 to 5% of cattle native to high altitudes and 10 to 40% of cattle adapted to low altitude and moved to higher altitudes for pasture grazing (Will and Alexander, 1970; Salman et al., 1990). Heritability estimates for PAP from nonrefereed sources range from 0.40 to 0.46 (LeValley, 1978; Schimmel, 1981; Enns et al., 1992), suggesting pulmonary arterial pressures (PAP) may be reduced in successive generations by selection. This in turn would be expected to reduce the incidence of brisket disease.

Research conducted by Schimmel and coworkers determined PAP were positively correlated with preweaning performance in heifer calves and negatively correlated with postweaning performance in feedlot bulls (Schimmel et al., 1980; Schimmel and Brinks, 1982, 1983). Correlations of PAP with growth are especially

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important, because genetic merit for direct effects on weaning and yearling weights in the national population of registered Angus cattle has been increasing over the last 3 decades at 1.5 and 2.8 kg·yr⁻¹, respectively (American Angus Association, 2007). Darling and Holt (1999) found coefficients from parent-offspring regression of PAP were different for sire-daughter compared with sire-son, dam-daughter, and dam-son comparisons. Possible explanations include maternal effects or different inheritance of PAP for male and female calves. The objectives of this study were to compare alternative models of PAP to quantify genetic and phenotypic relationships between PAP and growth traits of Angus weaned calves bred and tested at an altitude of 1,981 m.

MATERIALS AND METHODS

Animal Care and Use Committee approval was not obtained for this study, because data were obtained from existing databases.

Data Source

A database of PAP scores from a Colorado ranch located at an elevation of 1,981 m was made available by the owner. Body weights and pedigree information from that ranch were provided by the American Angus Association. Both data sources were provided electronically in 2004. Body weights had been collected from 2,305 spring-born, registered Angus cattle born between 1984 and 2003. Cattle included 1,088 bulls, 1,150 heifers, and 67 steers that were AI or natural-mated progeny of 132 sires and 793 dams. Average progeny per sire and dam were 16 and 2, respectively.

Adjusted Weaning Weight

Adjusted 205-d weaning weight (**WW**) was calculated as birth weight (**BWT**) plus 205 × ADG from birth to weaning (Beef Improvement Federation, 2002), with no adjustment for age of dam. No adjustments were made to BWT.

Measurement of PAP

A single measure of PAP from each calf was collected at weaning in November of each year, except 2003, when PAP was measured in December. The same licensed veterinarian experienced in PAP measurement collected scores on an average of 115 animals·yr⁻¹ using procedures described by Ahola et al. (2006). In brief, a catheter was inserted into either jugular vein via venipuncture and threaded through the right atrium and ventricle to the pulmonary artery. Systolic and diastolic blood pressures were measured and averaged using a cardiac monitor (Hewlett-Packard, Grady Medical Systems, Winchester, CA). Age at the time of PAP testing averaged 277 d, ranged from 171 to 343 d with a SD of 28 d, and was used as a linear covariate for PAP.

Multivariate Models for PAP

Three multivariate models were compared, which differed in the nature of the random effects for PAP but used commonly accepted model equations for WW and BWT. Fixed effects fitted for growth traits were identified from previously published reports and included contemporary group effects defined as management group × age of dam × year × sex subclasses. Fixed effects for PAP included age of dam, contemporary group defined as year × sex subclasses, and the covariate age at measurement. These were tested for significance in a single-trait mixed model using a conditional Wald statistic in ASREML (Gilmour et al., 2006). Significant fixed effects were subsequently fitted for PAP in multivariate models including growth traits.

The model equations for growth traits included direct (D superscript) and maternal (M superscript) effects and were $y_{BWT} = cg_{BWT} + u_{BWT}^D + u_{BWT}^M + e_{BWT}$ and $y_{WW} = cg_{WW} + u_{WW}^D + u_{WW}^M + e_{WW}$, where cg_i and e_i denote the contemporary group and residual effects for trait i . Model 1 included the 2 growth trait equations and a maternal model equation for PAP, $y_{PAP} = cg_{PAP} + \beta a_{PAP} + u_{PAP}^D + u_{PAP}^M + e_{PAP}$. The coefficient β represented the regression of PAP on age at PAP measurement, a_{PAP} . Model 2 included the 2 growth trait model equations and 1 equation for PAP measurements on males (PAPM) and another for measurements on females (PAPF), $y_{PAPM} = cg_{PAPM} + \beta_M a_{PAPM} + u_{PAPM}^D + e_{PAPM}$, and $y_{PAPF} = cg_{PAPF} + \beta_F a_{PAPF} + u_{PAPF}^D + e_{PAPF}$. These equations for PAP did not include maternal effects. A distinct regression coefficient, β_i , was fitted for age at PAP measurement, a_{PAPi} , where i reflects the sex of the animal with the PAP record. Model 3 was the simplest model for PAP and included the 2 growth trait model equations and a model equation for PAP that ignored maternal effects and did not distinguish random direct and residual effects according to the sex of the animal with the PAP record, $y_{PAP} = cg_{PAP} + \beta a_{PAP} + u_{PAP}^D + e_{PAP}$.

The residual variance-covariance matrices for models 1 and 3 were constructed from a matrix \mathbf{R}_0 of order 3 and included 6 parameters. The corresponding matrix for model 2 had order 4 and included 9 parameters, not counting the residual covariance between PAPM and PAPF, because no individual could be observed for both the male and female definition of the trait.

The genetic variance-covariance matrices were constructed from a matrix \mathbf{G}_0 that for model 1 had order 6 ($u_{BWT}^D, u_{BWT}^M, u_{WW}^D, u_{WW}^M, u_{PAP}^D, u_{PAP}^M$), model 2 had order 6 ($u_{BWT}^D, u_{BWT}^M, u_{WW}^D, u_{WW}^M, u_{PAPM}^D, u_{PAPF}^D$), and model 3 had order 5 ($u_{BWT}^D, u_{BWT}^M, u_{WW}^D, u_{WW}^M, u_{PAP}^D$). The corresponding number of genetic parameters was 21, 21, and 15, making a total of 27, 30, and 21 variance parameters in each of the 3 models.

Models were compared by likelihood ratio test, assuming that the genetic and residual effects followed a multivariate normal distribution with zero covariance between genetic and residual effects. Twice the absolute

difference, after convergence, in ASREML-estimated likelihood between the full and reduced models was compared with tabulated χ^2 values with degrees of freedom determined by the difference in number of parameters between the models. The significance of maternal effects for PAP was obtained from the likelihoods for models 1 and 3. This test had 6 df, the difference in number of parameters between the 2 models. The significance of fitting PAP as different traits by sex could not be obtained by comparing likelihoods of models 1 and 3, because these have different fixed effects and ASREML does not compute the contribution of fixed effects to the likelihood. Instead, model 3 was approximated by parameterizing model 2 using converged estimates of variance parameters from model 3 and assessing the likelihood without iteration. The genetic correlation between male and female effects could not be parameterized to unity, because this would result in a singular genetic variance-covariance matrix. Accordingly, it was fixed as 0.99, arbitrarily close to the boundary of the parameter space. This test had 9 df.

Variance components were estimated using significant fixed effects for PAP and the most appropriate multivariate model. Functions of estimated components, such as heritabilities and genetic and phenotypic correlations, were obtained from converged variance components using ASREML procedures.

RESULTS AND DISCUSSION

Average BWT and WW were 36.6 ± 0.1 kg and 224.1 ± 0.6 kg, respectively. Measurements of PAP were collected when calves were 277 ± 0.6 d of age, and scores averaged 39.8 ± 0.2 mmHg. Previously reported mean PAP scores were slightly lower, ranging from 32.1 to 38.6 mmHg in Angus bulls and heifers, but were observed at slightly higher altitudes of 2,070 to 2,316 m (Schimmel et al., 1980, 1981; Schimmel and Brinks, 1983; Enns et al., 1992).

Age of dam was not a significant effect for PAP ($P > 0.7$), and was therefore not included as a fixed effect in the PAP model equation for variance component estimation.

Heritability for PAP was 0.34 ± 0.05 , whereas heritabilities for direct and maternal BWT and WW were low to high (Table 1) but consistent with literature estimates. Heritabilities and genetic correlations among direct and maternal BWT and WW will not be discussed further, because there are already numerous published estimates (Garrick et al., 1989; Speidel et al., 2007) and reviews (e.g., Koots et al., 1994a,b). Maternal heritability for PAP converged to the boundary of 0.0. The model with maternal genetic effects for PAP was not significantly better ($P > 0.7$) than a model with only direct effects. Previous heritabilities for single measures of PAP collected at weaning ranged from 0.13 to 0.46 (Schimmel et al., 1981; Schimmel, 1981; Enns et al., 1992), and the current estimate, 0.34, was within this range. Heritability estimates for repeated PAP mea-

surements tend to be greater. LeValley (1978) estimated PAP heritability to be 0.42 and 0.66 when measured at birth and weaning, respectively, for a pooled data set of purebred Hereford and Angus cattle at an elevation of 2,316 m. Schimmel (1981), at the same elevation, estimated high and consistent heritabilities, 0.77 and 0.78, for pre- and postweaning measurements of PAP in a pooled data set comprising purebred Hereford, Angus, and Red Angus bull calves.

Heritabilities for PAP scores evaluated in females and males as distinct, but genetically correlated, traits were 0.38 ± 0.07 and 0.46 ± 0.09 , respectively. In females, measurements of PAP increased 0.022 ± 0.008 mmHg·d⁻¹ of age, whereas in males, PAP decreased 0.004 ± 0.01 mmHg·d⁻¹. The genetic correlation between female and male PAP was 0.64 ± 0.12 with no significant improvement in likelihood ($P > 0.4$), suggesting PAP measurements in females and males are the same trait. Darling and Holt (1999) found evidence of a positive sire-offspring relationship for PAP scores on sires and their sons and a negative relationship between PAP scores on sires and their daughters. Dam-offspring relationships with bull or heifer calves were positive and of similar magnitude in their study.

Genetic correlations between PAP and weights were positive and large for direct effects and close to zero for maternal effects (Table 1). Schimmel (1981) reported genetic correlations with PAP of -0.43 and 0.19 , for birth and weaning weights, respectively. Phenotypic correlations between PAP and weights were positive but low (Table 2). LeValley (1978) reported phenotypic correlations of -0.20 and 0.05 , for BWT and WW, respectively. Collectively, these reports suggest correlations between PAP and growth traits may be sensitive to age or season in which PAP was measured.

Brisket disease is most prevalent in fall and winter, because a decrease in ambient temperature, occurrence of inclement weather, or both, is more common than in spring and summer (Jensen et al., 1976a,b; Busch et al., 1985). Calves exposed to colder temperatures in a temperature-controlled hypobaric chamber developed pulmonary hypertension, and exposure to high altitudes exacerbated this condition further (Busch et al., 1985). The hypobaric chamber mimicked conditions calves may experience when moved to higher-altitude pastures in midsummer. Alexander and Jensen (1959) and Alexander et al. (1960) observed variation in susceptibility of calves to brisket disease when dams were moved to higher elevations prepartum. Subsequent studies at an altitude of 1,524 m observed variation in postpartum survival among those calves with elevated PAP at birth. Some died within 10 d, whereas others exhibited a gradual decrease then stabilization in PAP scores over the same time frame (Will et al., 1975a,c; Stenmark et al., 1987). These results suggested there may be both individual and maternal influence on PAP.

In the current study, greater PAP scores did not appear to be adversely phenotypically associated with WW. Every animal whose details were provided for

Table 1. Heritability (on diagonal) and genetic correlations (above diagonal; \pm SE) among pulmonary arterial pressure (PAP), birth weight direct and maternal (BWTD and BWTM), and weaning weight direct and maternal (WWD and WWM) for spring-born, registered Angus cattle

Trait	PAP	BWTD	BWTM	WWD	WWM
PAP	0.34 \pm 0.05	0.49 \pm 0.12	0.01 \pm 0.17	0.51 \pm 0.18	-0.05 \pm 0.14
BWTD	—	0.45 \pm 0.08	-0.12 \pm 0.18	0.36 \pm 0.18	0.09 \pm 0.15
BWTM	—	—	0.14 \pm 0.04	0.33 \pm 0.26	0.15 \pm 0.17
WWD	—	—	—	0.16 \pm 0.06	-0.44 \pm 0.18
WWM	—	—	—	—	0.26 \pm 0.05

analysis had a WW. Colorado ranchers usually move cows and calves before weaning to grazing pastures at higher altitudes in June or July, and susceptible calves that did not exhibit symptoms at birth may have developed brisket disease (Will et al., 1975a,b) and died before weaning with no birth information being entered into the database. The extent of such bias cannot be determined from these records.

Alexander and Jensen (1963) observed a phenotypic correlation between chronic hypoxia and hypertrophy of the smooth muscle located within pulmonary arteries and arterioles. Comparison of domestic cattle and other *Bos* species residing at high altitudes indicated the latter do not experience brisket disease, even though these animals reside at altitudes of 3,200 m or higher (Anand et al., 1986; Durmowicz et al., 1993). Durmowicz et al. (1993) evaluated the response of the native high-altitude yak (*Bos grunniens*) and determined that at rest at 730 m the yak had PAP scores of 24 mmHg, lower than 29 mmHg for yearling steers residing at 1,600 m and 24 mmHg for cattle less than 1 yr of age at sea level. Durmowicz et al. (1993) also observed that induced hypoxia elevated PAP, but a vasoconstrictor agent such as norepinephrine caused greater vasoconstriction response and higher PAP than hypoxia. Also, acetylcholine and sodium nitroprusside caused vasodilation, lowered PAP, and increased cardiac output.

Comparison of domestic cattle and yak artery and arterioles indicated the yak had less vascular smooth muscle, and endothelial cells were longer, wider, and rounder. Histological differences may influence pulmonary vascular tone and reactivity and allow the yak to adapt to hypoxic conditions better than cattle (Durmowicz et al., 1993). Anand et al. (1986) mated adapted high-altitude yak sires with domestic cows, and the F₁ progeny had PAP and pulmonary arterial resistance measurements similar to yak sires; however, backcrossing F₁ females with domestic bulls created backcross progeny with segregated PAP scores representative of either the resistant yak or susceptible domestic cow. Anand and coworkers (1986) concluded the F₁ and some backcross progeny retained the hypoxic hypovasoconstrictor response of the high-altitude yak. Will et al. (1975a) observed a similar result in which progeny of sires resistant to high-altitude pulmonary hypertension

and brisket disease had calves that were resistant and had lower PAP scores than progeny of susceptible sires.

Regulation of variation in the vasoconstrictor response by a single locus may be plausible; however, the challenge will be to determine where the locus is and what gene or genes are influenced by that locus. Comparison of smooth muscle in the small pulmonary arteries and arterioles indicated a negative relationship between the amount of smooth muscle and hyporesponsiveness (Tucker et al., 1975). Therefore, smooth muscle structure may be useful to identify proteins responsible for regulation of pulmonary hypertensive reactivity and expression of brisket disease. Potential candidates include plasminogen activator, endothelial NO synthase, and hypoxia-inducible factor-1.

Plasminogen activator is a protein associated with repair of the endothelial cells of veins and capillaries. Astrup et al. (1968) observed greater mean levels of this protein in *Bos indicus* vs. *Bos taurus* cattle, suggesting *B. indicus* are less susceptible to brisket disease and are able to recover more quickly if inflicted. Polymorphisms induced in the endothelial NO synthase gene resulted in mice that were more reactive to mild hypoxia and developed pulmonary hypertension more quickly than mice lacking the polymorphisms (Stuedel et al., 1997). Levels of hypoxia-inducible factor-1 were shown to influence expression of genes that modify vascular tone in response to low oxygen tension (Ke and Costa, 2006). Variation in pulmonary hypertensive reactivity is present among many species, and other candidate genes may be identified using genomes of the hyper-responsive porcine, moderately responsive rodent, hyporesponsive ovine, or nonresponsive canine (Tucker et al., 1975).

Table 2. Phenotypic (below diagonal) and residual (above diagonal) correlations (\pm SE) and phenotypic SD (on diagonal) for pulmonary arterial pressure (PAP), birth weight (BWT), and weaning weight (WW) for spring-born, registered Angus cattle

Trait	PAP	BWT	WW
PAP	8 mmHg	-0.17 \pm 0.06	-0.13 \pm 0.05
BWT	0.10 \pm 0.03	4 kg	0.28 \pm 0.06
WW	0.02 \pm 0.03	0.35 \pm 0.04	26 kg

Regardless of the underlying causes of variation, single measures of PAP collected in spring-born registered Angus cattle were found to be moderately heritable but had unfavorable genetic correlations with direct effects on growth. 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. Selection for performance at high altitude should consider PAP along with growth and other economically relevant traits recorded in high-altitude conditions.

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