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The altitude at which a calf is born and raised influences the rate at which mean pulmonary arterial pressure increases with age[1]

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ABSTRACT: Right heart failure secondary to pulmonary hypertension is a leading cause of mortality among suckling beef calves in the Rocky Mountain region. The objective of this study was to track changes in pulmonary arterial pressures (PAP) in healthy calves born and raised at altitudes ranging from 1,470 to 2,730 m. It was hypothesized that calves located at higher altitudes would show a greater increase in mean PAP (mPAP) with age than would be experienced by calves located at lower altitudes. The rationale is that high altitude hypobaric hypoxia causes a greater rate of vascular remodeling and, consequently, greater resistance to blood flow than calves located at lower altitudes. A prospective study was conducted on 5 cohorts of suckling calves from 4 herds located at altitudes of 1,470, 2,010, 2,170, and 2,730 m. In total, 470 PAP measurements were obtained from 258 calves. As hypothesized, calves located at altitudes ≥2,170 m showed a significant increase in mPAP with age ($P \leq 0.002$) whereas calves at 1,470 m did not ($P = 0.16$). Except for calves at 2,170 m ($P < 0.001$), systolic PAP did not increase with age ($P \geq 0.16$). Diastolic PAP increased with age at altitudes ≥ 2,170 m ($P \leq 0.09$) but did not change in calves at 1,470 m ($P = 0.20$). In summary, mPAP and the rate at which mPAP increases with age are positively associated with the altitude at which calves are born and raised.

Key words: beef, hypoxia, pulmonary hypertension, right heart failure

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INTRODUCTION

Right heart failure (**RHF**) secondary to pulmonary hypertension is a leading cause of mortality in suckling beef calves on mountainous ranches in the Rocky Mountain region (Neary et al., 2013b). The positive association between altitude and mean pulmonary arterial pressure (**mPAP**) in cattle was first reported in the early 1960s (Will et al., 1962). It is thought that cattle with mPAP over 49 mmHg are high-risk candidates for RHF (Holt and Callan, 2007). Previous research suggests that the incidence of RHF in spring-born calves may be greatest in the fall because mPAP increase with age (Neary et al., 2013a). To our knowledge, however, it is not known how pulmonary arterial pressures (**PAP**) change with age in suckling calves born and raised at different altitudes. This information would make an important contribution toward resolving the complex pathogenesis of pulmonary hypertension and heart failure in suckling calves.

The objective of this study was to evaluate PAP in healthy calves born and raised at altitudes ranging from 1,470 to 2,730 m. It was hypothesized that calves

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located at higher altitudes would show a greater increase in mPAP with age than would be experienced by calves located at lower altitudes. The rationale is that the hypobaric hypoxia of high altitude causes a greater rate of vascular remodeling than calves located at lower altitudes.

MATERIALS AND METHODS

Study Overview

A prospective study was conducted on 5 cohorts of suckling calves from 4 herds located at altitudes ranging from 1,470 to 2,730 m. Pulmonary arterial pressures (mean, systolic, and diastolic) were evaluated twice within the same year in 4 cohorts but just once in 1 cohort. Two of the calf cohorts from the same herd were evaluated over 2 consecutive years; this provided information regarding year-to-year variation in mPAP. This study received approval from the Colorado State University Animal Care and Use Committee before the sampling or handling of any animals (protocol 09-1524A).

Study Sites and Cattle

Four herds were enrolled in this study: 3 herds located in Colorado (at altitudes of 1,470, 2,010, and 2,730 m) and 1 herd located in southern Wyoming (at an altitude of 2,170 m). The herds situated at 2,010, 2,170, and 2,730 m were commercial cow–calf operations and consisted of Red Angus and Hereford crossbred cattle; Black and Red Angus; and Red Angus, Hereford, Gelbvieh, and Simmental composites, respectively. Black Angus seedstock calves were studied at 1,470 m. Calves were clustered into 5 cohorts for statistical analyses. These cohorts were sampled in either 2011 or 2012 (Table 1). Calves sampled at 2,730 m formed 2 cohorts: calves born and sampled in 2011 and calves born and sampled in 2012. Every second calf that entered into the chute was sampled.

The dams of calves studied were given a prebreeding and precalving vaccination offering protection against viral agents of respiratory disease. Calves were vaccinated against the same respiratory pathogens at 4 to 8 wk of age and 2 to 4 wk before weaning. A hormonal growth promotant (Synovex C; Zoetis, Madison, NJ) containing 100 mg progesterone and 10 mg estradiol benzoate was administered to all calves in the herd at 2,730 m when approximately 8 wk old.

The herds at 1,470 and 2,010 m only used breeding bulls with mPAP less than 45 mmHg at their respective altitudes. Approximately 50% of the calves at an altitude of 2,170 m were progeny of bulls with a yearling mPAP <40 mmHg. The other 50% of the calves were progeny of industry relevant AI sires of unknown mPAP. Calves at 2,730 m were progeny of bulls with mPAP <42 mmHg at 2,440 m.

Table 1. The altitude, date of sampling, number of calves sampled, sex, and mean age of the 4 herds studied[1]

Altitude, m	Date	Number sampled[2]				Mean age (SD), d
		Hef	Bul	Ste	Tot	
1,470	July 1, 2011	17	13	0	30	131 (16)
	Oct. 27, 2011	17	11	0	28	250 (16)
2,010	Sept. 27, 2011	17	0	13	30	126 (13)
2,170	July 31, 2012	0	55	5	60	124 (18)
	Oct. 1, 2012	0	55	5	60	187 (18)
2,730	June 27, 2011	44	11	25	80	91 (7)
	Oct. 12, 2011	40	10	23	73	199 (7)
	June 21, 2012	30	0	28	58	86 (7)
	Oct. 10, 2012	27	0	24	51	197 (7)

[1]Calves that died between test periods were removed from the study. Calves missing at random at the second test, due to missing ear tag identification, for example, remained in the study.

[2]Hef = heifers; Bul = bulls; Ste = steers; Tot = total.

The majority of calves were tested on 2 occasions approximately 3 mo apart, between the months of June and October (Table 1). It is unlikely that environmental temperatures affected PAP measurements; temperatures ranged from 9 to 24°C. Calves at 2,010 m were tested only once because herd management practices could not accommodate repeated sampling. A total of 470 PAP measurements were obtained from 258 calves. Calves known to have died in the period between testing were removed from the data. Calves missing at random on the second test day, due to lost ear tag identification, for example, remained in the data.

Pulmonary Arterial Pressure Testing

A full description of the equipment, materials, and facilities required for PAP testing is provided by Holt and Callan (2007). In brief, a 12-gauge, 8.9-cm needle was inserted into the jugular vein. Flexible, saline-filled, polyethylene catheter tubing (external and internal diameter of 17 and 12 mm, respectively) was then fed through the needle, into the right atrium and ventricle, and then into the pulmonary artery. A pressure transducer connected the catheter to an oscilloscope (BM5Vet; Bionet America, Inc. Tustin, CA). The position of the catheter tip within the vascular system was determined from the pressure waveform on the oscilloscope. The jugular vein, right atrium, right ventricle, and pulmonary artery have distinct pressure waveforms (Holt and Callan, 2007). Mean, systolic, and diastolic pressures were recorded after the pulmonary pressure waveforms stabilized. Pulse pressure was calculated as the absolute difference between systolic and diastolic pressures. Calves were corralled

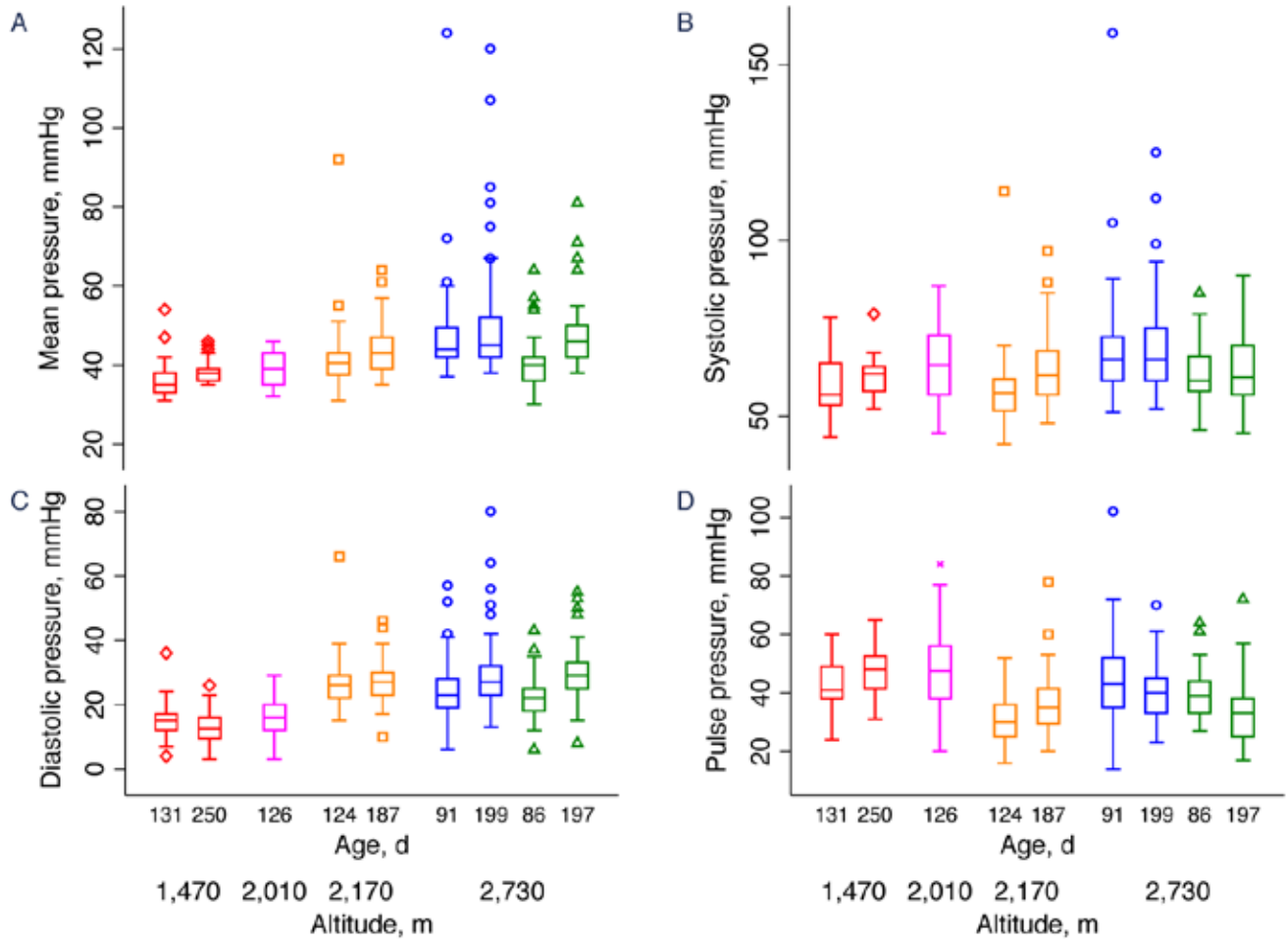

Figure 1. Box and whisker plot of (A) mean pulmonary arterial pressures, (B) systolic pulmonary arterial pressures, (C) diastolic pulmonary arterial pressures, and (D) pulmonary arterial pulse pressures of healthy calves according to age (d) and altitude (m). Hollow symbols represent outliers (observations that are greater than 1.5 times the interquartile range from the nearest quartile). Red, magenta, orange, blue, and green colors indicate calves sampled at altitudes of 1,470, 2,010, 2,170, 2,730 (year 2011), and 2,730 m (year 2012).

for at least 20 min before sampling; therefore, it was unlikely that physical exertion had any effect on PAP.

Statistical Analyses

Statistical analyses were performed using STATA version 12 (Stata Corporation, College Station, TX). Statistics are presented as mean and 95% confidence interval (**CI**) of the mean unless otherwise indicated. Descriptive summaries of PAP are provided as box and whisker plots stratified by the altitude and mean age of the calves sampled. Calves at an altitude of 2,010 m were sampled just once and, therefore, were not included in subsequent analyses.

Generalized estimating regression equations were used to estimate PAP (mean, systolic, diastolic, and pulse) in association with age and calf cohort (a proxy for altitude) while controlling for sex (heifer, steer, or bull). Age × cohort interactions were evaluated in all models. This regression method is robust to missing observations and accounts for lack of independence associated with repeated measures (Liang and Zeger, 1986; Zeger and Liang, 1986). An exchangeable correlation structure was used; this structure assumes the same correlation between all pairs of observations. Adjusted mean estimates of PAP were obtained for each of the 5 cohorts from 100 to 200 d of age while controlling for sex.

Pairwise Pearson correlation analyses were used to evaluate the relationship of PAP (mean, systolic, diastolic, and pulse) between tests. A Bonferroni correction was applied to achieve a family wise error rate of 0.05 for all pairwise analyses.

RESULTS

Descriptive Summary

Mean PAP and diastolic PAP (**dPAP**) showed positive associations with altitude (Fig. 1A and 1C), but systolic PAP (**sPAP**) and pulse pressure did not (Fig. 1B and 1D). On average, calves at higher altitude had greater mPAP than calves at a lower altitude (Fig. 2A). Diastolic

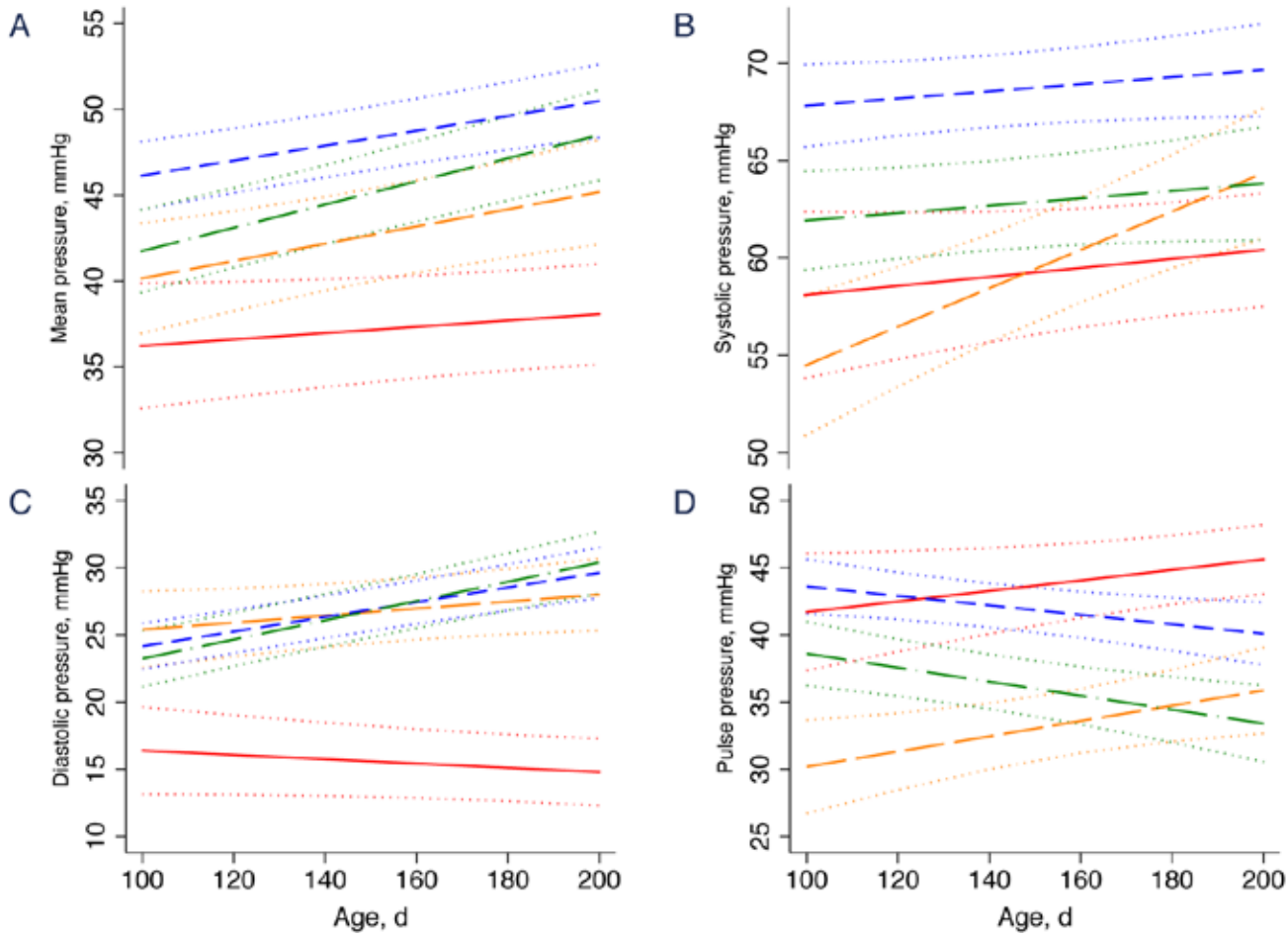

Figure 2. Line graph showing adjusted means and 95% confidence intervals (dashed lines) for (A) mean pulmonary arterial pressure, (B) systolic pulmonary arterial pressure, (C) diastolic pulmonary arterial pressures, and (D) pulmonary arterial pulse pressure, with age in suckling calves at altitudes of 1,470 (solid red line), 2,170 (long-dash orange line), and 2,730 m in 2011 (dashed blue line) and 2012 (long-dash dot green line).

PAP, on the other hand, did not increase incrementally with altitude (Fig. 1C). In 4-mo-old calves, dPAP were approximately 10 mmHg greater at 2,170 and 2,730 m than at 1,470 and 2,010 m (Table 2). Of all the pulmonary pressures measured in calves at 2,730 m, dPAP was the most consistent between the years 2011 and 2012. Systolic PAP and pulse pressure did not show a significant relationship with altitude (Fig. 1B and 1D). For sPAP, however, this was largely due to wide variation about the mean (Fig. 2B; Table 2). The greatest and least mPAP were 124 (altitude of 2,730 m) and 31 mmHg (altitude of 1,470 m), respectively. The former calf showed moderate distension of the jugular vein, indicative of elevated right atrial pressure, but no other signs of ill health.

Changes in Pulmonary Arterial Pressure

There were significant age × cohort interactions for all PAP measurements when controlling for sex: mPAP ($P = 0.03$), sPAP ($P = 0.01$), dPAP ($P < 0.001$), and pulse pressure ($P < 0.001$). Sex was not statistically associated with any of the PAP ($P \geq 0.24$). In 2011, 4-mo-old calves at 2,730 m had mPAP 11 mmHg greater than calves at 1,470 m when controlling for sex (Table 2). This difference increased with increasing age. Calves located at altitudes ≥2,170 m experienced an increase in mPAP with age, whereas calves at 1,470 m did not (Fig. 2A). For every 100 d, mPAP increased by 2 mmHg at 1,470 m (95% CI = –1 to 0; $P = 0.16$), 5 mmHg at 2,170 m (95% CI = 2 to 8; $P = 0.002$), 4 mmHg at 2,730 m in 2011 (95% CI = 3 to 6; $P < 0.001$), and 7 mmHg at 2,730 m in 2012 (95% CI = 5 to 9; $P < 0.001$).

Diastolic PAP increased with age at altitudes ≥2,170 m but did not change in calves at 1,470 m (Fig. 2C). For every 100 d, dPAP changed by –2 mmHg at 1,470 m (95% CI = –4 to 0; $P = 0.20$), 3 mmHg at 2,170 m (95% CI = 0 to 6; $P = 0.09$), 5 mmHg at 2,730 m in 2011 (95% CI = 4 to 7; $P < 0.001$), and 7 mmHg at 2,730 m in 2012 (95% CI = 5 to 9; $P < 0.001$).

Systolic PAP showed a significant altitude × age interaction because calves at 2,170 m showed a 10 mmHg increase over the course of 100 d (95% CI = 6 to 14; $P < 0.001$; Fig. 2B). Calves at all other altitudes, however, experienced an increase in sPAP of only 2 mmHg over

Table 2. Adjusted pulmonary arterial pressures at 4 mo of age when controlling for sex

Altitude, m	Year	Mean (95% confidence interval)[1]			
		mPAP	sPAP	dPAP	Pulse pressure
1,470	2011	36[a] (33–40)	58[a] (54–62)	16[a] (13–19)	42[ab] (38–46)
2,010	2011	39[ab] (35–42)	64[ab] (59–68)	16[a] (13–20)	47[a] (43–51)
2,170	2012	41[ab] (38–44)	57[a] (54–60)	26[b] (24–29)	31[c] (28–34)
2,730	2011	47[c] (45–49)	68[b] (66–70)	25[b] (24–27)	43[a] (41–45)
2,730	2012	43[bc] (41–45)	62[a] (60–65)	25[b] (23–27)	38[b] (35–40)

[a–c]Within a row, values without a common superscript differ ($P < 0.05$).

[1]mPAP = mean pulmonary arterial pressure; sPAP = systolic pulmonary arterial pressure; dPAP = diastolic pulmonary arterial pressure.

Table 3. Pearson pairwise correlation coefficients for pulmonary arterial pressure in clinically healthy calves obtained at approximately 4 and 7 mo of age

Altitude, m	Year	Pearson correlation coefficient[1]			
		mPAP	sPAP	dPAP	Pulse pressure
1,470	2011	0.14	–0.19	0.25	–0.09
2,170	2012	0.87*	0.23	0.40*	0.00
2,730	2011	0.60*	0.35*	0.58*	–0.02
2,730	2012	0.65*	0.26	0.49*	–0.05

[1]mPAP = mean pulmonary arterial pressure; sPAP = systolic pulmonary arterial pressure; dPAP = diastolic pulmonary arterial pressure.

*Correlations with P-value < 0.05.

100 d ($P \geq 0.16$). For every 100 d, sPAP increased by 2 mmHg at 1,470 m (95% CI = –1 to 6; $P = 0.21$), 2 mmHg at 2,730 m in 2011 (95% CI = –1 to 4; $P = 0.16$), and 2 mmHg at 2,730 m in 2012 (95% CI = –1 to 5; $P = 0.20$).

Pulse pressure increased with age in calves at 1,470 and 2,170 m but decreased in calves at 2,730 m (Fig. 2D). For every 100 d, pulse pressure changed by 4 mmHg at 1,470 m (95% CI = 0 to 8; $P = 0.06$), 6 mmHg at 2,170 m (95% CI = 0 to 10; $P = 0.02$), –3.5 mmHg at 2,730 m in 2011 (95% CI = –6 to 0; $P = 0.02$), and –5 mmHg at 2,730 m in 2012 (95% CI = –8 to 2; $P = 0.002$).

Pairwise Correlation of Pulmonary Arterial Pressures between Tests

Mean PAP and dPAP were moderately correlated between tests performed at approximately 4 and 7 mo of age in herds located at altitudes of 2,170 and 2,730 m (Table 3). Systolic PAP and pulse pressure showed weak, if any, correlation between tests irrespective of altitude (Table 3). None of the PAP variables were correlated between tests in calves at 1,470 m.

DISCUSSION

The results of this study indicate that the altitude at which a calf is born and raised influences the rate at which mPAP increases with age. As hypothesized, calves in herds at higher altitudes showed a greater age-related increase in mPAP than calves in herds located at lower altitude (1,470 m); the latter showed no change in mPAP with age.

These findings may have important implications for the beef industry, particularly the feedlot industry of the Great Plains. It has been suggested that yearling feedlot cattle originating from mountainous regions are more susceptible to RHF, or brisket disease, than cattle sourced from lower altitudes (Jensen et al., 1976). Perhaps, as our results suggest, this is because cattle originating from mountainous regions enter feedlots with pulmonary arteriolar vessel narrowing and remodeling, consistent with hypoxia-induced pulmonary hypertension, than cattle originating from lower altitudes. Although the vascular lesions associated with pulmonary hypertension in cattle may be somewhat reversible (Alexander et al., 1965), steers that have a greater than average mPAP as a suckling calf at high altitude tend also to have a greater than average mPAP as fat steers ready for slaughter (Neary et al., 2015). Combined, these studies suggest that altitude of origin may be an important consideration when managing the risk of RHF at the feedlot; epidemiological and histopathological studies are, however, necessary to further evaluate this.

In addition, we observed minority populations of animals with outlying high pulmonary pressures in all herds; the dispersion of outliers worsened with increasing pasturage elevations (Fig. 1). This variation may in part reflect genetic mechanisms (Shirley et al., 2008; Zeng et al., 2014). In this regard, we and our collaborators recently described a gain of function polymorphism in the *hypoxia inducible factor-2* (*EPAS1*) gene that predisposes beef cattle raised at high elevations to increased PAP (Newman et al., 2015). This polymorphism was detected in approximately 30% of animals in unselected herds and, therefore, may contribute to our results. Moreover, extensive studies in neonatal calves exposed to environmental hypoxia (14 d, equivalent to 4,300 m) have demonstrated that pulmonary vascular adventitial fibroblasts are durably converted to a proinflammatory phenotype through epigenetic mechanisms (El Kasmi et al., 2014; Wang et al., 2014). These findings have been confirmed in experimental rodent models and in human clinical pulmonary hypertension (Zhao et al., 2012). Taken together, these findings suggest that the combination of genetic predisposition plus epigenetic history predisposes individuals to maladaptive pulmonary hypertension, vascular remodeling, and increased risk of RHF in response to chronic alveolar hypoxia. Prospective identification of susceptible animals through genetic testing and assessment of blood-based biomarkers may provide benefits in economic productivity for producers.

The positive association between mPAP and age in calves at higher altitudes (≥2,170 m) was attributable to age-related increases in dPAP but not sPAP. Except for 1 herd, sPAP increased very little with increasing age. Diastolic PAP, on the other hand, increased at a greater rate in calves at higher altitudes. This may have been attributable to a greater rate of pulmonary vascular remodeling, elevated heart rates, progressive left ventricular dysfunction, or a combination of such factors occurring in calves at higher altitudes. Increasing heart rate can cause dPAP to rise because the reduced interval between ventricular contractions leaves less time for PAP to fall. This may be particularly true when vascular resistance is high, due to hypoxic pulmonary vasoconstriction, for example (Enson et al., 1977). In the present study, hypoxia-induced vascular remodeling, alone or in combination with an age-related increase in heart rate, likely contributed to the greater age-related increase in dPAP in higher altitude herds. By including simultaneous measurements of heart rate and PAP, future studies will be able to determine the importance of heart rate on dPAP.

Another plausible reason for the age-related increase in dPAP in higher altitude herds is progressive left ventricular dysfunction. In humans free of obstructive pulmonary lesions, dPAP was found to be positively correlated ($r \geq 0.70$) with left ventricular end-diastolic pressure (Falicov and Resnekov, 1970). To our knowledge, it is not known if dPAP is correlated with left ventricular end-diastolic pressure in cattle, particularly when an animal is experiencing pulmonary hypertension. There is, however, some evidence that pulmonary venoconstriction or left ventricular dysfunction may contribute to the development of pulmonary arterial hypertension in cattle (Kuida et al., 1963; Busch et al., 1985).

Possible causes of left ventricular dysfunction include ventricular interference associated with right ventricular enlargement (Taylor et al., 1967; Louie et al., 1995), myocardial edema secondary to increased coronary venous pressure (Watanabe et al., 1990; Dongaonkar et al., 2012), and reduced left ventricular compliance due to direct effects of hypoxia on the myocardium (Gomez and Mink, 1986; Kullmer et al., 1995; Boussuges et al., 2000; Kjaergaard et al., 2006). Detailed physiological studies are necessary to determine the role of the left ventricle, if any, in the development of pulmonary arterial hypertension.

A limitation of this study is that confounding at the herd level may have occurred with factors such as herd management, climate, and genetics. This limitation, however, was necessary to successfully meet the goal of this study, which was to evaluate PAP changes in suckling calves born and raised at their respective altitudes. The notable differences in PAP obtained from the same herd (2,730 m) over consecutive years indicates that the confounding effects of management, climate, and other unknown factors might have been considerable. According to the nearest weather station (Crested Butte, CO), there was greater precipitation during the summer months (May to September) in the year 2012 (16.76 cm) than in the year 2011 (10.2 cm; Colorado Climate Center, 2015). Given that, for unknown reasons, RHF is more problematic in wet pastures than dry (Glover and Newsom, 1915; Hecht et al., 1959; Hull and Anderson, 1978), it is plausible that greater summer rainfall in the year 2012 might have contributed to the greater age-related increase in mPAP relative to the previous dryer summer.

In summary, the altitude at which a calf is born and raised influences the rate at which mPAP increases with age. Calves born at the highest altitudes showed the greatest increase in mPAP with age and calves born at the lowest altitude showed the least. The age-related increase in mPAP that occurred in higher altitude herds was primarily attributable to an increase in dPAP. The underlying mechanisms for the increase in dPAP are unclear. Although hypoxia-induced vascular remodeling likely played a significant role, we cannot rule out the possibility that other physiological factors, such as heart rate and left ventricular dysfunction, contributed to the age-related increase in mPAP in calves at higher altitudes.

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