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Evaluating the Epidemiology and Management of Bovine Congestive Heart Failure

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by

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A form of congestive heart failure is increasingly reported as a cause of death in feedlot cattle located at moderate altitude (1524 m. or less). Significant knowledge gaps exist in the epidemiology and management of this form of bovine congestive heart failure (BCHF) regarding frequency and timing of BCHF cases and ways in which beef cattle producers and veterinarians can mitigate this condition. These knowledge gaps present major barriers to understanding the mechanism of BCHF and mitigating the consequences of BCHF in cattle. The purpose of this thesis is to summarize what is currently known about BCHF, define gaps in knowledge for which more research is needed, formulate hypotheses regarding the knowledge gaps, and discuss two studies designed to test those hypotheses related to the emergence of BCHF. The first study presented is designed to estimate the frequency and timing of BCHF case development. The second study was completed to evaluate the effect of moving two bulls affected by pulmonary arterial hypertension from their ranch of origin to lower elevation as a possible management strategy for mitigation of pulmonary arterial hypertension. Results presented in this thesis provide evidence that the frequency of BCHF cases has increased over the course of six years in the feedlot studied and changing the environment of animals affected by pulmonary arterial hypertension by moving them to a location of lower altitude than their origination point can lead to a decrease in pulmonary arterial pressure. This thesis will interpret the results of both studies to highlight how these data can aid in understanding the underlying mechanism of BCHF.

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CHAPTER 1: LITERATURE REVIEW

Evaluating the epidemiology and management of bovine congestive heart failure

Adam S. Bassett, DVM

ABSTRACT

Bovine congestive heart failure (BCHF) is increasingly reported as a cause of death in feedlot cattle located at less than 1524 m. elevation. Many cases of BCHF develop in beef cattle that are in the finishing stages of the production cycle. BCHF was first characterized in moderate altitude feedlots in the 1970s. Since then, evidence supports an increase in BCHF case incidence. BCHF is a terminal condition and producers are left with few options for mitigation of BCHF. Due to the increase in incidence and lack of management or treatment options, BCHF presents a significant animal welfare problem and poses economic concerns for beef producers. Significant knowledge gaps exist in epidemiology and management of BCHF regarding frequency and timing of BCHF case development and ways in which beef cattle producers and veterinarians can mitigate this condition. The purpose of this literature review is to summarize what is currently known about BCHF and to define gaps in knowledge for which more research is needed.

INTRODUCTION TO BOVINE CONGESTIVE HEART FAILURE

Bovine congestive heart failure (BCHF) is increasingly reported as a cause of death in feedlot cattle at moderate elevations (335 – 1524 m). BCHF was first documented in feedlot cattle at moderate altitude in the 1970s and has since been reported to be increasing in frequency (Jensen et al., 1976a; Jensen et al., 1976b; Neary et al., 2016). Clinical signs of BCHF include ventral subcutaneous edema, pendulous abdomen, and jugular distension and/or pulsation (Reef and McGuirk, 2015). Postmortem lesions noted at necropsy include enlargement of the right ventricle of the heart, liver congestion ("nutmeg" liver), ascites, and pleural effusion (Moxley et al., 2019). Histopathologic lesions associated with BCHF include interstitial myocardial fibrosis, myocyte hypertrophy, cardiac adipose deposition, and pulmonary venous remodeling (Krafsur et al., 2019; Moxley et al., 2019). Bovine congestive heart failure is a terminal condition and may present considerable economic concerns for cattle producers, particularly in areas such as western Nebraska, eastern Colorado, and eastern Wyoming (https://nebraskacattlemen.org/wp-content/uploads/2019/01/ncpolicyforncba.pdf). For the purposes of this literature review, the acronym BCHF will be used to designate the form of congestive heart failure occurring in feedlot cattle at moderate altitude.

Known etiologies of congestive heart failure (CHF) in cattle are exposure to hypobaric environments, traumatic reticulopericarditis, infectious endocarditis, lymphoma, ionophore toxicity, and congenital heart diseases such as ventricular septal defects. BCHF in feedlots does not appear to be associated with congenital disease, infectious endocarditis, lymphoma, or traumatic reticulopericarditis because no signs of

these diseases have been noted on necropsy of fulminant BCHF cases (Krafsur et al., 2019; Moxley et al., 2019).

Ionophore toxicity has been considered as a possible etiology for BCHF. Clinical signs in cattle recently exposed to toxic doses of ionophores mirror those seen in feedlot BCHF (Van Vleet et al., 1983). Findings at necropsy for cases of ionophore toxicity include myocardial necrosis and hemorrhaging in conjunction with necrosis of skeletal muscle and the diaphragmatic muscle (Van Vleet et al., 1983; Van Vleet and Ferrans, 1983). These findings may be seen grossly, but are confirmed with histopathology. However, no hemorrhaging or necrosis of cardiac, skeletal, or diaphragmatic muscle has been noted grossly at necropsy of BCHF cases and lesions characteristic of ionophore toxicity have not been reported in histopathological studies of tissues from BCHF cases (Krafsur et al., 2019; Moxley et al., 2019).

Of all of the known etiologies for CHF, BCHF appears to be most similar to high altitude disease or CHF secondary to hypoxia-induced pulmonary arterial hypertension because of its presenting clinical signs and there is evidence that pulmonary arterial hypertension may lead to BCHF development (Moxley et al., 2019). High altitude disease was first reported in the literature over 100 years ago by Glover and Newsom (Glover and Newsom, 1914). In Glover and Newsom's (1914) report, animals affected with CHF at high altitude (2133 m. or above) present with the characteristic signs of right-sided congestive heart failure including subcutaneous edema, ascites, and jugular venous distension or pulsation. Later work showed that pulmonary arterial hypertension predisposes cattle to development of CHF at high altitudes (Hecht et al., 1962; Holt and Callan, 2007). Glover and Newsom (1914) also showed that an effective management

strategy for high altitude disease was to transport affected animals to lower elevation (typically ~ 1524 m.), resulting in a resolution of clinical signs. Due to the efficacy of moving affected animals to lower elevations, this management strategy has been implemented in many high altitude beef production systems.

Moxley et al. (2019) hypothesized that BCHF develops secondary to hypoxia-induced pulmonary arterial hypertension in cattle located at moderate altitudes (Moxley et al., 2019). Seventeen cattle that developed right-heart failure at one feedlot in western Nebraska over the course of 15 months were included in their postmortem study. Histopathological analysis was done on various tissues from each of the animals. Tissues analyzed in the study included heart, lung, liver, and kidney. Lesions noted at necropsy and on histopathology were consistent with hypoxia-induced pulmonary arterial hypertension, particularly intimal hyperplasia of pulmonary elastic arteries. Moxley et al. (2019) report that in 9 of 17 cases, signs of pneumonia were absent despite the presence of hypoxia-induced lesions (Moxley et al., 2019). This suggests that, while pneumonia can cause hypoxia that leads to pulmonary arterial hypertension, the lesions noted in many of the cattle in their study are due to some other cause of hypoxia leading to pulmonary arterial hypertension.

The epidemiology of BCHF remains a subject of investigation. Currently there are two epidemiological studies investigating BCHF. Of the two epidemiological studies regarding BCHF, the earliest is a survey evaluating diseases that occur in yearling feedlot cattle (Jensen et al., 1976a; Jensen et al., 1976b). Jensen et al. surveyed four Colorado feedlots weekly throughout the year 1974 (Jensen et al., 1976b). Total number of cattle fed in 1974 across all four feedlots surveyed was 407,000 animals. On average, the

feedlots included in the Colorado survey were located at about 1584 m. elevation. Disease diagnoses were based on necropsies done each week in each of the four feedlots surveyed. Survey results from all four feedlots showed, from a total of 1,988 necropsies performed in 1974, BCHF was diagnosed 116 times.

The second epidemiological study, conducted by Neary et al. (2016), investigated the risk over time of developing right-heart failure and risk factors for right-heart failure case development in feedlots located from southern Alberta to the Texas Panhandle (Neary et al., 2016). Twelve years' worth of data from fifteen individual feedlots were analyzed. In total, the data included 1.56 million cattle. The years 2000, 2004, 2008, and 2012 were specifically analyzed for right-heart failure incidence and risk factors. Data from these years provide evidence that the risk of right-heart failure in feedlot cattle had nearly doubled from 0.21/1000 cattle to 0.40/1000 cattle between the years 2000 and 2012.

Factors evaluated by Neary et. al. (2016) as possible risk factors for development of right-heart failure were season of cattle placement in the feedlot, risk of development of bovine respiratory disease (BRD) or undifferentiated fever (UF), age, sex, and status of treatment for BRD. Neary et al. (2016) showed cattle classified as having a high risk for development of BRD or UF were 2-3 times more likely to die of right-heart failure (Neary et al., 2016).

Genetic factors have long been suspected as a possible etiology for BCHF (Hecht et al., 1962; Jensen et al., 1976a; Newman et al., 2015; Heaton et al., 2019). Newman et al. (2015) conducted a study in which they determined that a variant of the *EPAS1* gene is

associated with development of pulmonary arterial hypertension, ultimately leading to high altitude CHF (Newman et al., 2015). However, the Newman study did not include cattle that develop CHF at elevations comparable to that at which BCHF occurs (~335 – 1524 m.). To test the hypothesis that *EPAS1* is the gene involved in BCHF case development, Heaton et al. (2019) conducted a case control study in which 36 *EPAS1* haplotype combinations were evaluated from 102 case-control pairs (Heaton et al., 2019). The findings of the Heaton (2019) study show that the *EPAS1* gene is not associated with BCHF development. Therefore, while the evidence supports *EPAS1* involvement in the high-altitude form of CHF, further research is needed to determine which gene or genes are associated with BCHF.

Pathophysiologic mechanisms have been proposed, but remain untested. Krafsur et al. (2019) hypothesized regarding the pathophysiology of BCHF in feedlot cattle located in western Nebraska, northeast Colorado, and southeast Wyoming stating that intensive fattening leads to left ventricular fibrosis and intracardiac adipose deposition (Krafsur et al., 2019). Krafsur et al. (2019) did detailed histopathological analyses of cardiopulmonary and hepatic tissue samples collected at necropsy examination of 15 yearling cattle showing signs of BCHF from commercial feedlots. Their histopathological results showed lesions of left ventricular fibrosis and intracardiac adipose deposition. The presence of left ventricular fibrosis and intracardiac adipose increases the diastolic filling pressure of the left ventricle, leading to left ventricular remodeling and pulmonary venous hypertension. When the pathological effects on the left side become overwhelming, remodeling of the whole pulmonary vascular network begins, ultimately leading to development of pulmonary arterial hypertension and right sided heart failure.

However, exactly when in the course of disease the left ventricular fibrosis and intracardiac adipose deposition develops remains unclear.

Similar to high altitude CHF, hypoventilation and hypoxia have been proposed as possible etiologic and pathophysiologic mechanisms for BCHF, respectively (Jensen et al., 1976a). Jensen et al. (1976a) proposed that hypoventilation may be caused when feedlot cattle have full rumens and are recumbent (Jensen et al., 1976a). According to their hypothesis, recumbency may cause the full rumen to exert pressure on the diaphragm, decreasing thoracic space. The decreased thoracic space may then lead to rapid, shallow respiration and hypoventilation. After prolonged periods of hypoventilation, hypoxia would ensue, and pulmonary arterial hypertension would ultimately develop similarly to high altitude CHF. No other evidence exists to support this hypothesis.

Jensen et al. (1976a) also proposed the possibility that rapid growth in feedlot cattle could lead to development of pulmonary arterial hypertension and ultimately BCHF (Jensen et al., 1976a). Feedlot cattle spend a considerable amount of time eating, which maximizes their growth. Rapid growth could increase the work load of the heart, ultimately leading to failure. However, Neary et al. (2016) showed that, while half of the BCHF cases included in their study did occur after 19 weeks on feed, BCHF cases occurred at all times throughout the feeding period (Neary et al., 2016). Given the current epidemiologic data available, no clear association between growth rate and BCHF risk has been identified.

Effective management strategies for BCHF in feedlot cattle continue to be elusive. However, one management strategy exists related to high altitude CHF. Glover and Newsom (1914) mention that from their own experience and the experiences of many high altitude producers in the early 20th century, removal of CHF affected animals from high altitude (> 2133 m.) to a lower altitude (< 1524 m.) was an effective management strategy, citing a resolution of clinical signs as evidence (Glover and Newsom, 1914). The success of this management strategy has led to its implementation by high altitude producers for handling cases of pulmonary arterial hypertension and fulminant CHF.

DEFINING THE GAPS IN KNOWLEDGE

As very few studies have been done regarding the frequency and timing of BCHF cases in feedlots (Jensen et al, 1976a; Neary et al., 2016), more information addressing this knowledge gap is needed. Having a more complete understanding of the frequency and timing of BCHF will aid in characterization of the underlying mechanism of disease by providing data regarding the onset of BCHF cases and when the various pathologic changes develop during the course of disease.

Glover and Newsom (1914) observed that moving cattle to lower altitude effectively reduced or eliminated the clinical signs of high altitude disease in affected animals (Glover and Newsom, 1914). Currently, there are few if any options for handling BCHF in feedlots at moderate altitudes. Glover and Newsom's report is the first documentation of high altitude disease in beef cattle and, at the time, many of the same knowledge gaps existed for high altitude disease that currently exist for BCHF. Given that Glover and Newsom were able to elucidate a management strategy to address one

form of congestive heart failure, it may be possible that an effective management strategy could exist for BCHF in feedlot cattle as well.

This thesis will describe the findings of two studies; one is an epidemiological investigation designed to examine the frequency and timing of case development in cattle located in one feedlot in western Nebraska. The second study is a case report describing the hemodynamic and hematologic effects of transportation of two bulls diagnosed with pulmonary arterial hypertension from an elevation of ~1219 m. to an elevation of ~518 m. Characterization of the timing and frequency of incident BCHF cases will contribute to understanding the mechanism of disease providing information about the sequence of disease timing. Understanding hemodynamic and hematologic effects of transporting cattle with pulmonary hypertension to lower elevations will provide insight into a possible management strategy for cattle affected with pulmonary arterial hypertension and will help to characterize the pathophysiological mechanism of moderate altitude pulmonary arterial hypertension and potentially BCHF.

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CHAPTER 2: EPIDEMIOLOGY

Trends in Case Development for Bovine Congestive Heart Failure in Feedlot Cattle at one Feedlot

Adam S. Bassett, DVM and Brian L. Vander Ley, DVM PhD

Abstract

Bovine congestive heart failure (BCHF) is emerging as a leading cause of death in feedlot cattle located at moderate altitude (914 -1524 m.). The purpose of this study is to characterize the frequency and timing of incident BCHF cases. Knowledge of disease frequency and timing is a critical step in elucidating the sequence of events that culminates in clinical disease and in understanding the etiology of the disease. Six years of records from one feedlot containing 111,329 cattle were retrospectively evaluated and trends in case development were determined. Prior to initiation of this study, evidence supported an increase in frequency of BCHF since the first report of BCHF at moderate altitude in the 1970s. After analyzing data from one feedlot, results of this study are consistent with previous reports that case frequency is increasing. Characterization of disease frequency and timing is a critical step in elucidating the sequence of events that culminates in clinical disease and in understanding the etiology of the disease.

Introduction

Congestive heart failure (CHF) is a condition in beef cattle that has been known to exist in North America for over 100 years (Glover and Newsom, 1914). For the majority of that time, one form of CHF, known as high altitude disease, was thought to only occur in beef cattle that are grazed at altitudes of 2133 m. or greater (Glover and Newsom,

1914). In the 1970s, a condition with clinical attributes similar to those of high altitude disease was documented in feedlots located in eastern Colorado (altitude ~ 1524 m. or lower) (Jensen et al., 1976). Currently known as bovine congestive heart failure (BCHF), this condition continues to be diagnosed in moderate altitude feedlots (914 – 1524 m.).

Neary et al. investigated the incidence of right-heart failure (RHF) in fifteen separate feedlots in North America by retrospectively examining health records from 1.56 million cattle during four separate years in a twelve-year time span (Neary et al., 2016). Neary's study primarily focused on changes in RHF incidence over time and investigated potential risk factors for RHF development. Although data from feedlots from across North America were included, Neary's study focused primarily on Canadian feedlots. Data from United States (U.S.) feedlots was only included for one year out of the four examined. Results of their study show the risk of RHF doubled in the Canadian feedlots and, despite having only one year of data from U.S. feedlots, cattle in U.S. feedlots were at double the risk of developing RHF compared to cattle in Canadian feedlots. However, as only one year of data was examined for U.S. feedlots, and only four years were examined in total, having more data on a year to year basis may be useful for making conclusions about the incidence of RHF in U.S. feedlots.

The purpose of this study is to determine the frequency and trends of BCHF cases. Two hypotheses are tested in this study; first, BCHF case frequency has increased over time; second, BCHF occurs exclusively in cattle that are nearing the end of their feeding periods. Characterization of disease frequency and timing is a critical step in elucidating the sequence of events that culminates in clinical disease and in understanding the etiology of the disease.

Materials and Methods

The participating feedlot provided summary information for each lot fed between 2011 and 2016. This summary information consisted of arrival date, shipment date, number of cattle received and number of cattle shipped. Information about individual cases was also compiled including individual identification, lot number, date of diagnosis, and whether the animal died or was culled prematurely (realized).

Table 2.0 Summary of data utilized for this study. Table represents the total number of lots that left the feedlot within each year, the total number of head that entered the feedlot within each year, and the total number of bovine congestive heart failure (BCHF) cases that developed within each year. The bottom row represents the totals for each category over the course of the six-year period.

YEAR	NUMBER OF LOTS	NUMBER OF HEAD IN	NUMBER OF CASES
2011	192	14285	56
2012	367	24168	60
2013	268	18729	103
2014	240	18385	99
2015	230	20188	116
2016	221	15556	120
Total	1518	111,329	554

Study Population

The study population consisted of cattle placed in one commercial feedlot in western Nebraska over the course of the years 2011-2016. This feedlot was chosen for analysis because of prior history of high BCHF incidence at this feedlot, availability of records, and prior relationships formed with this feedlot on other research studies.

Information from a total of 111,329 cattle that entered this feedlot over the six-year period ending in December of 2016 was included in the data analysis (see table 2.0).

Disease Diagnosis

Bovine congestive heart failure was defined as any animal showing one or more antemortem clinical signs of congestive disease including ventral subcutaneous edema, abduction of the elbows, jugular pulse, and dyspnea. Diagnoses were made by experienced animal caretakers. All animals with an antemortem diagnosis of BCHF that died were necropsied by a veterinarian or by trained feedlot personnel and confirmed as a BCHF case if observed lesions included ascites, pleural edema, ventral subcutaneous edema, and congestive lesions of the heart and liver with no other possible etiology for the lesions identified. Of notable importance, not every diagnosed BCHF case died. Some of the BCHF case animals were culled prematurely and sent to harvest. Some animals with early signs of BCHF, but near established endpoints, were shipped to harvest early. In these cases, the animal was often not recorded as a BCHF case and could potentially contribute to an erroneous apparent reduction in the frequency of cases at the very end of the feeding period. The diagnosis was recorded in the shipment and death records maintained by the feedlot.

Statistical Analysis

Analysis was performed using the histogram and pivot table functions of Microsoft Excel. Using these functions, the proportion of cases by year (of lot close-out), proportion of cases by month of diagnosis, proportion of cases by days after feedlot entry, number of cases per 100,000 head days on feed, proportion of cases by days until lot

harvest, and proportion of cases by degree of finish was determined. Case data was provided for the years 2011-2016. Pivot tables were created to summarize the frequency and proportion of cases by year and month of case diagnosis. This information was then plotted as a histogram. The cases/100,000 head days, proportion of cases by month of diagnosis, proportion of cases by days after feedlot entry, proportion of cases by days until lot harvest, and proportion of cases by degree of finish are expressed in histograms in figures 2.1-2.5, respectively. Refer to table 2.1 for a description of how the calculations for cases/100,000 head days, days until lot harvest, and degree of finish were defined.

Table 2.1 Explanation of how cases/100,000 head days and percent of cases by degree of finish (percent finished by days on feed) were calculated. DOF = Days on feed. See figures 2.1 and 2.5, respectively.

Variable	Definition/Formula
Cases/100,000 Head Days	$\frac{Frequency\ of\ Cases\ per\ Lot}{\#\ of\ Days\ per\ Head\ within\ Lot} * 100000$
Days to Lot Harvest	$Lot\ End\ Date - DOF\ at\ Diagnosis$
Degree of Finish (% Finished)	$\frac{DOF\ at\ Diagnosis}{Lot\ End\ Date - Lot\ Start\ Date}$

Results

Proportion of Cases by Year (of lot closeout)

Figure 2.0 is a histogram representing the proportion of BCHF cases by year (of lot closeout).

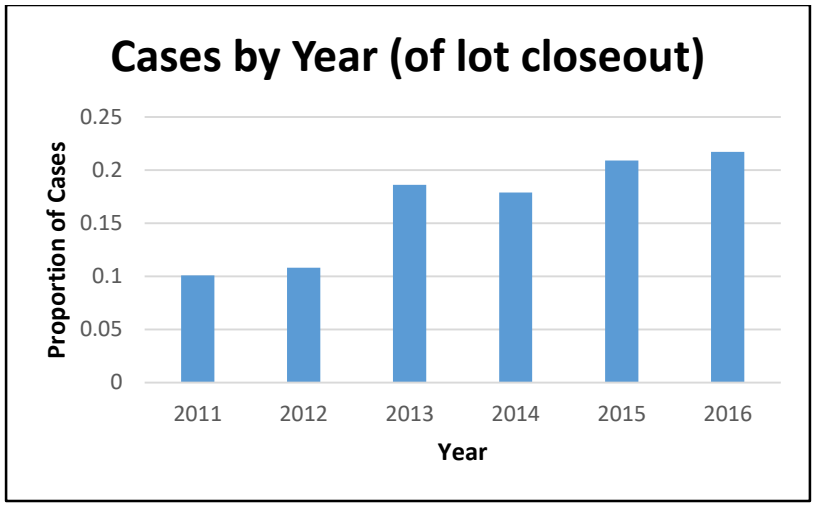

Figure 2.0 Proportion of cases by year.

Cases per 100,000 Head Days on Feed

Figure 2.1 shows the number of cases per 100,000 head days at risk.

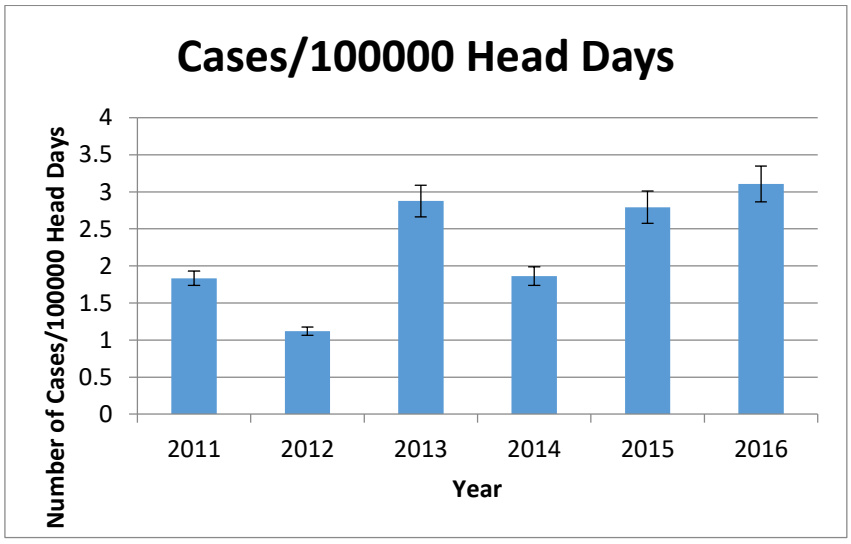

Figure 2.1 Frequency of cases per head per day at risk. Error bars show the 95% confidence interval with $P < 0.05$.

Proportion of Cases by Month of Diagnosis

Figure 2.2 shows the frequency of BCHF cases by month of diagnosis for lots that closed out in 2011-2016.

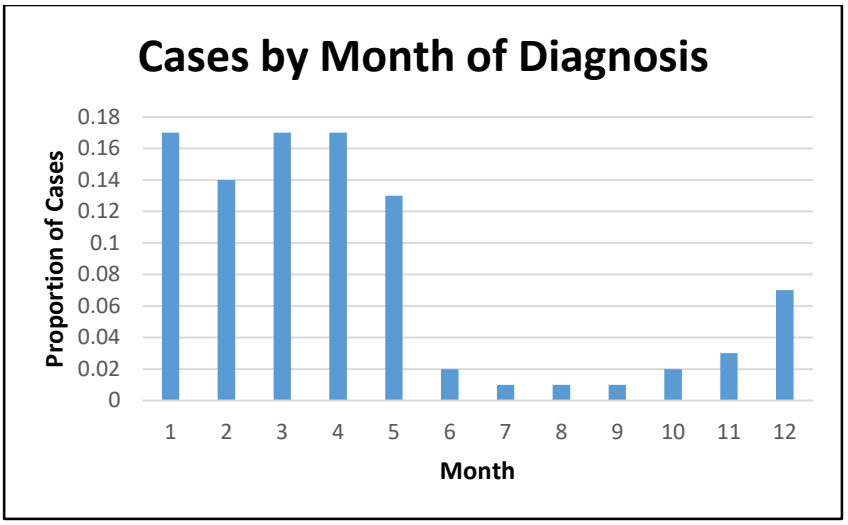

Figure 2.2 Proportion of cases by month of diagnosis. Numbers for each month correlate to month of the year (1=January – 12=December).

Proportion of Cases by Days after Feedlot Entry

Figure 2.3 shows the proportion of cases by days after feedlot entry.

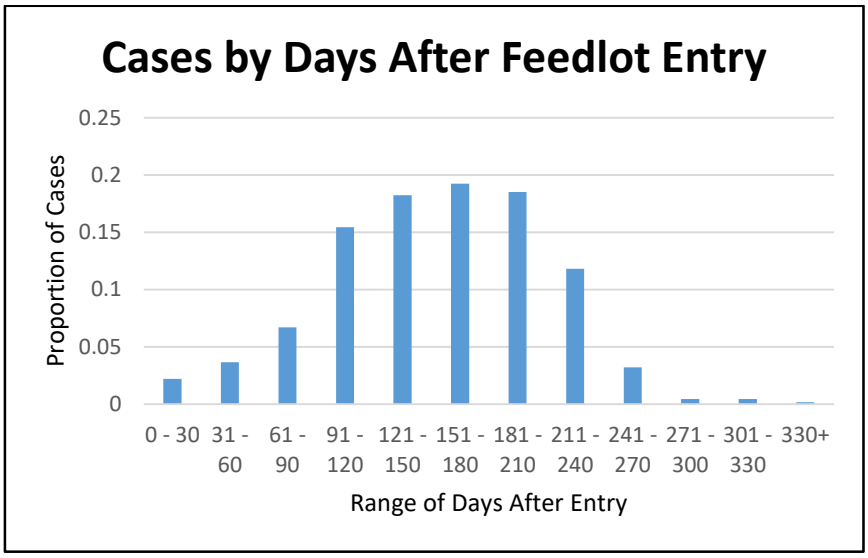

Figure 2.3 Proportion of cases based on days after feedlot entry.

Proportion of Cases by Days Until Lot Harvest

Figure 2.4 shows the proportion of cases by days until lot harvest.

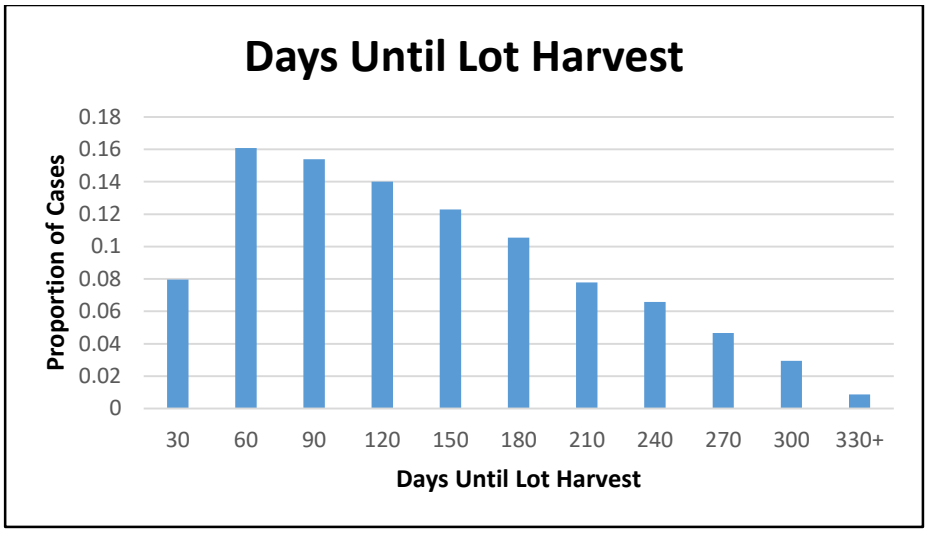

Figure 2.4 Frequency of cases that developed by days until lot harvest.

Proportion of Cases by Degree of Finish

Figure 2.5 shows the proportion of cases by degree of finish.

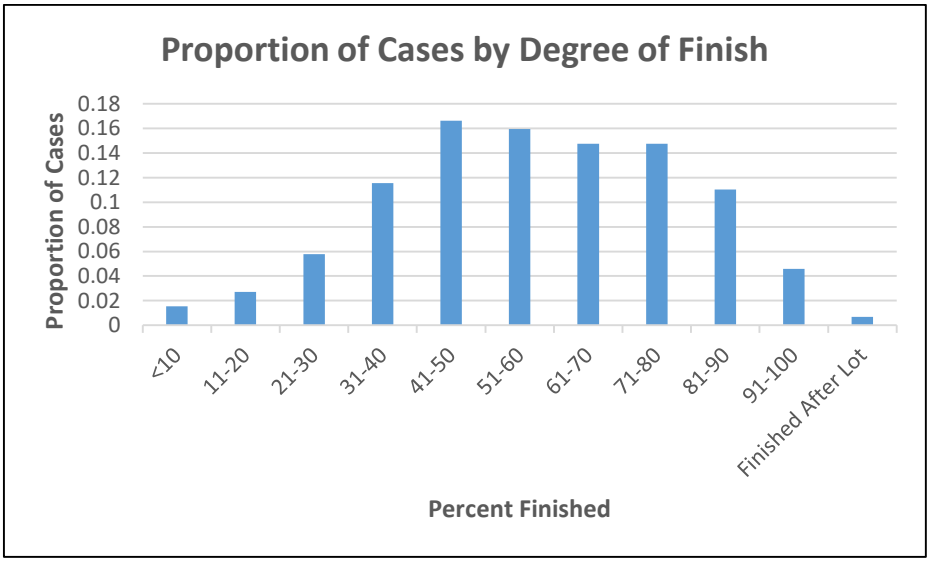

Figure 2.5 Proportion of cases by degree of finish.

Discussion

The number of cases per 100,000 head days on feed (figure 2.1) increases each year during the observation period, after accounting for changes in number of cattle fed and time at risk. The increasing trend is interrupted by a decrease in incident cases from 2013 to 2014. While these numbers may reflect natural variation in the incidence of BCHF, cattle flow into and out of the feedlot was significantly altered immediately prior to and during the anomalous years. Severe drought in 2012 resulted in early weaning of calves and subsequent early placement in the feedlot. Calves arrived at a lighter weight and required more time to reach market weight. The lengthened time in the feedlot shifted the time at risk so that cases that may have otherwise developed in 2012 were actually diagnosed in 2013, resulting in an apparent increase in incident cases in 2013. Despite this anomaly, the results fail to reject that frequency of BCHF cases has been increasing over the six years studied.

Most BCHF cases develop early in the year, with the majority of cases diagnosed between January and May (Figure 2.2). This trend is most likely due to the cyclical nature of cattle placement in feedlots. Each year, calves are born in the spring, are weaned and shipped to feedlots in the fall, and finish in late spring or early summer of the following year. As a result, many feedlots are usually filled to capacity during the late winter and spring months of each year, which maximizes the population at risk of developing BCHF.

Another possible explanation for the increased frequency of cases in the early months of the year could be weather effects (Jensen et al., 1976). The late winter and early spring months in western Nebraska are known for having a wide range of

unpredictable weather. This includes blizzards in the late winter months and severe thunderstorms in the spring. Producers have observed that rapidly changing weather, especially the onset of severe weather, seems to precipitate an increase in new case development. Jensen et al. (1976) also observed an increase in case development in the fall and winter following severe weather (Jensen et al., 1976).

Data from this study indicate that BCHF cases occur at all stages of the feeding period (Figures 2.3, 2.4, and 2.5). These data are consistent with a previous report that indicated distribution of incident cases throughout the feeding period, albeit with increased concentration of cases after 19 weeks in the feedlot (Neary et al., 2016). Analysis of timing of incident cases relative to arrival, harvest, and progress toward market weight (degree of finish) indicates that many BCHF cases occur in the mid to later stages of the feeding period. However, there are many BCHF cases that develop in the early stages of the feeding period. Neary et al. (2016) hypothesized that cases occurring late in the feeding period could be attributable to the accumulation of body fat over this period of time, ultimately leading to hypoventilation and alveolar hypoxia (Neary et al., 2016). Hypoventilation secondary to fat accumulation has previously been hypothesized to be a cause of BCHF development in feedlot cattle (Jensen et al., 1976). Krafsur et al. (2019) proposed an alternative hypothesis that fat deposition along with left ventricular myofibrosis were driving pulmonary venous remodeling and ultimately increased right ventricular effort that resulted in CHF (Krafsur et al., 2019). The data from our analysis are inconsistent with these hypotheses. If fat deposition were the sole etiology of BCHF, then few cases would be expected to occur in the early days of the feeding period. Given that almost all cattle have developed large fat deposits during late

stages of the feeding period, the incidence of BCHF would be expected to be much higher if fat deposition was the sole etiology.

A limitation of this data analysis is the data was obtained from one feedlot. Including more feedlots in the analysis would provide a more complete picture of the trends of BCHF case development by increasing the study population and the results would become more generalizable to the feedlot industry. However, the data from this feedlot represents a large number and a wide variety of cattle. While it would still be important to include more feedlots in the analysis, data from this feedlot provides insight into BCHF case incidence.

Results of this study fail to reject the hypothesis that BCHF case frequency has increased over the six years studied at this feedlot. However, results reject the hypothesis that BCHF case development is exclusive to cattle that are nearing the end of their feeding periods at this feedlot. Data from additional feedlots is needed to fully test these hypotheses.

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CHAPTER 3: MANAGEMENT

Hemodynamic and hematologic effects of altitude change on pulmonary hypertension in two bulls originating at moderate altitude

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Abstract

A form of bovine congestive heart failure (BCHF) is increasingly reported as a leading cause of death in feedlot cattle at moderate altitude (914 - 1219 m.). Significant knowledge gaps exist in management of BCHF. The objective of this case study was to evaluate the impact of reducing altitude on clinical outcomes of pulmonary arterial hypertension. We hypothesized that decreasing altitude would decrease pulmonary arterial pressure (PAP). To test this hypothesis, two bulls that previously were diagnosed with pulmonary arterial hypertension were transported from approximately 1219 m. elevation to approximately 518 m. elevation. Sequential hemodynamic and hematologic measurements were collected followed by euthanasia and postmortem examination. We were unable to reject our hypothesis that moving the bulls to a lower elevation would decrease PAP, with bull #1 decreasing from 55 mmHg to 40 mmHg and bull #2 decreasing from 74 mmHg to 45 mmHg. However, postmortem examination revealed extensive cardiac changes. More research is needed to develop effective management interventions for BCHF; however, results of this case study provide information regarding the impact that decreasing altitude has on hemodynamic and hematologic parameters in bulls affected by pulmonary arterial hypertension.

Introduction

Congestive heart failure (CHF) in beef cattle can have several noninfectious, infectious, and toxicologic etiologies. One particular noninfectious form of CHF occurring at high altitudes (> 2133 m.) was first formally described over 100 years ago (Glover and Newsom, 1914; Hecht et al., 1962). Beginning in the 1970's, reports began to emerge of CHF occurring in beef cattle in the feedlot setting at moderate altitude (914 -1219 m.) (Jensen et al., 1976). Known as bovine congestive heart failure (BCHF), this condition has no known etiology, but it has similar clinical signs to high altitude CHF. Bovine congestive heart failure is reported to occur all over the Great Plains region of the United States and Canada (~335 m. – 1524 m. elevation), suggesting that high altitude may not have a strong etiologic role (Neary et al., 2016).

Clinical signs of BCHF include ascites, dependent subcutaneous edema, dyspnea, and agitation. In high altitude congestive heart failure, these clinical signs are the manifestation of physiological compensation to decreased atmospheric oxygen concentration (Alexander and Jensen, 1959). Cattle typically avoid ventilation/perfusion mismatch by constricting pulmonary arterioles in hypoxic lung regions. When cattle are exposed to low atmospheric oxygen, this arterial vasoconstriction occurs throughout pulmonary circulation creating elevated pulmonary arterial pressure and increased load on the right ventricle of the heart (Alexander and Jensen, 1959). When this compensatory mechanism becomes overwhelming, pulmonary hypertension develops and eventually progresses to clinical CHF. Similar to the high altitude-induced form of CHF, hypoxia has been suggested as a potential cause for the elevated pulmonary arterial pressures

(PAP) seen in CHF affected cattle at moderate elevations (914 – 1524 m.) (Jensen et al., 1976; Reef and McGuirk, 2015; Moxley et al., 2019).

Glover and Newsom (1914) reported clinical improvement of high altitude CHF cases after transportation to lower altitude (Glover and Newsom, 1914). The improvement seen by Glover and Newsom (1914) would also have coincided with a decrease in pulmonary arterial pressure. Atmospheric oxygen concentration is higher at lower altitude. Therefore, the increased oxygen concentration may improve oxygenation of the lungs, relieve arterial constriction, and decrease pulmonary arterial pressure.

The purpose of this case report was to observe the physiological effects of bringing 2 bulls with pulmonary arterial hypertension from approximately 1219 m. elevation to approximately 518 m. elevation. The authors hypothesize that, similar to the high altitude-induced disease, the decrease in altitude will result in a decrease in pulmonary arterial pressure. Specific goals of this report were to evaluate hemodynamic and hematologic parameters over a 6-week period following relocation of the bulls to 518 m. elevation after which both bulls were euthanized and examined via necropsy for gross pathology.

Materials and Methods

All procedures and activities related to animals were approved by the University of Nebraska Institutional Animal Care and Use Committee prior to initiation of the study. Two bulls diagnosed with pulmonary arterial hypertension were included. Neither of the bulls had ever been exposed to elevations above 1219 m. prior to the initiation of the study.

The bulls were evaluated from May 5, 2018 to June 12, 2018. Throughout the evaluation period, the bulls were provided a diet designed to meet or exceed the maintenance recommendations of the National Research Council; however, they were not fed to maximize intake or growth (National Academies of Sciences and Medicine, 2016).

The study period began when the bulls were transported from an approximate elevation of 1219 m. to an approximate elevation of 518 m. Throughout the study period, the bulls were monitored daily by experienced livestock personnel and twice weekly by a veterinarian. Blood samples were collected two times per week. Blood was collected from the jugular vein and immediately transferred to evacuated blood collection tubes containing EDTA (Medtronic, Minneapolis, MN), serum separation gel (Medtronic, Minneapolis, MN), and RNA preservative (Tempus Blood RNA Tube, Grenier Bio-One, Kremsmünster, AT). The EDTA blood was used for CBC analysis using an Element HT5 Veterinary Hematology Analyzer (Heska, Loveland, CO). Arterial blood collection from the auricular artery using a one ml heparinized syringe (Sanguis Counting Kontrollblutherstellungs, Nümbrecht, DE) was attempted each time venous blood samples were collected; however, circumstances often precluded successful collection of arterial blood. After three attempts to collect arterial blood had been made, a heparinized venous sample was collected instead. The heparinized sample was immediately transferred to a CG4+ i-STAT cartridge (Abbott Point of Care Inc., Princeton, NJ) and analyzed using an i-STAT handheld blood analyzer (Abbott Point of Care Inc., Princeton, NJ).

Right-sided cardiac hemodynamic assessments were completed every 14 days during the study period using methods previously described (Holt and Callan, 2007).

Briefly, using aseptic technique, a polyethylene catheter was inserted through a large bore needle into the right jugular vein. The catheter was advanced down the jugular vein while simultaneously flushing it with isotonic saline to aid the advancement. To track the location of the catheter, pressure changes associated with each location were monitored during the advancement using a BM5 Patient Monitor (Bionet Co., Seoul, KR). Pressure profiles were collected in each of the following locations: distal jugular vein, right ventricle, and proximal pulmonary artery. Systolic, diastolic, and mean pressures were recorded at each location.

On the final day of the study period, the bulls were transported to the University of Nebraska - Lincoln Veterinary Diagnostic Center for euthanasia and tissue sample collection. Euthanasia, using captive bolt and subsequent exsanguination, was done according to the AVMA Guidelines (Leary et al., 2013). Following euthanasia, a gross necropsy evaluation was performed and tissues were collected from the lung (right caudal, right middle, and right cranial lobes), liver, right ventricular wall with papillary muscle, left ventricular wall with papillary muscle, moderator band, pulmonary artery and aorta.

The heart was rinsed with water and digital photographs were taken of the intact heart to document gross morphologic changes and facilitate future comparisons. The heart was then bisected into transverse sections to allow comparisons of ventricular wall thickness. Digital photographs were taken of the transverse view of the heart. Once photography was completed, the samples listed above from the heart were collected.

Results

Each of the hematological parameters evaluated with the BM5 Patient Monitor (Bionet Co., Seoul, KR) are shown in Table 3.0.

Table 3.0. Table 3.0 represents the date on which the hemodynamic parameters were measured and shows the results of each measurement (mean values are shown). The measurements were taken as the catheter passed through each respective location. Key for location abbreviations: Jug = jugular pressure; RV = right ventricular pressure; PAP = pulmonary articular pressure. Abbreviation n/a = not available; measurements were not available before 5/1 because they were not taken at that time; measurements were not available on 5/1 and 5/14 for Bull #2 due to inability to be certain an accurate measurement was obtained from those locations. Each parameter was measured in mmHg.

	Bull #1 (mmHg)			**Bull #2** (mmHg)		
Date	Jug	RV	PAP	Jug	RV	PAP
Before 5/1	n/a	n/a	55	n/a	n/a	74
5/1/2018	17	45	55	n/a	n/a	57
5/14/2018	16	21	48	33	n/a	34
5/29/2018	34	35	34	15	51	43
6/11/2018	31	24	40	16	27	45

All hematological parameters measured on complete blood count (CBC) were within published reference intervals with the exception of mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), mean platelet volume (MPV), hemoglobin (Hgb), hematocrit (HCT), and erythrocytes (RBC) (Figures 3.0-3.4) (Cornell University, 2014). All blood samples were collected from the left jugular vein to preserve the right jugular vein for hemodynamic analysis. For bull #2, complications arising from mild hematoma formation and bull behavior precluded blood sample collection for CBC analysis on two of the scheduled sample days. The days on which a blood sample was unable to be obtained for bull #2 are noted in the figures.

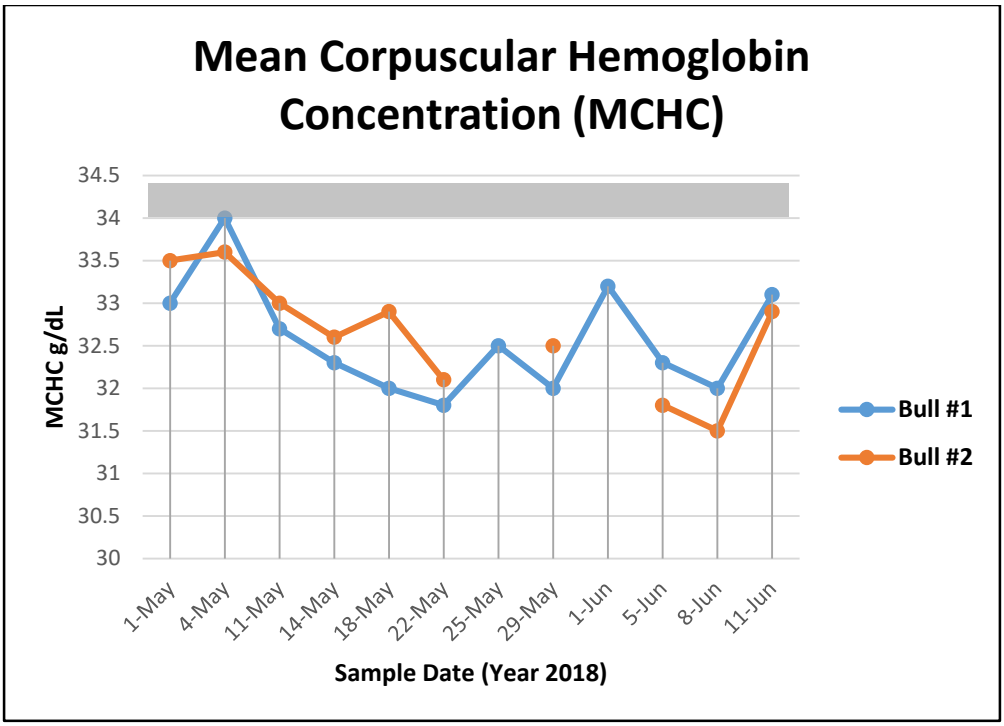

Figure 3.0 Results of mean corpuscular hemoglobin concentration on CBC. Reference interval used is 34 – 39 g/dL, as indicated by gray box on graph (Cornell University, 2014) . No sample was able to be obtained from bull #2 on 5/25 and 6/1.

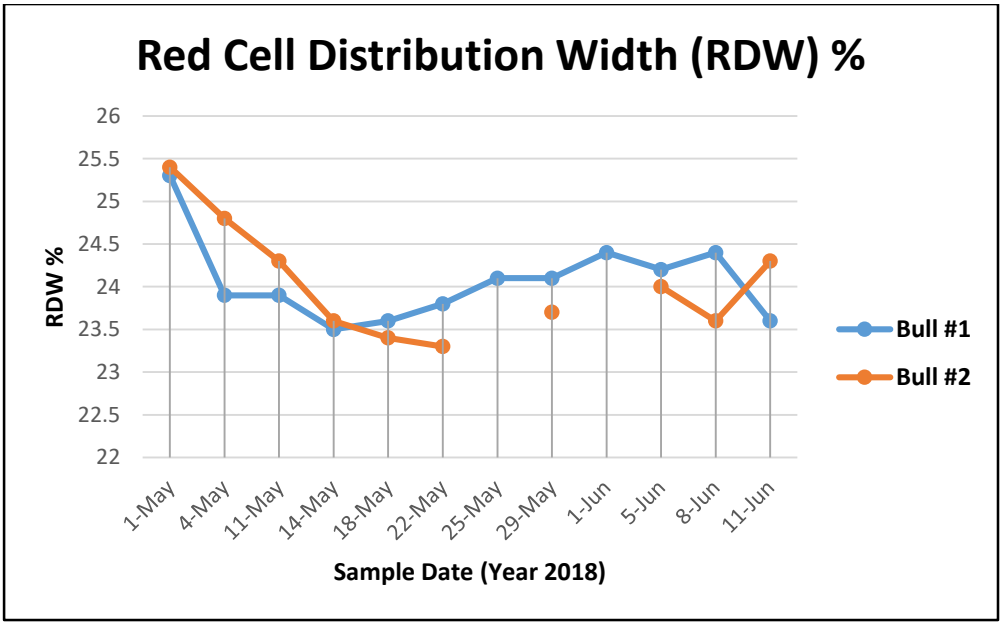

Figure 3.1 Results of red cell distribution width on CBC. Reference interval is 15 – 19.4% (Cornell University, 2014). No sample was able to be obtained from bull #2 on 5/25 and 6/1.

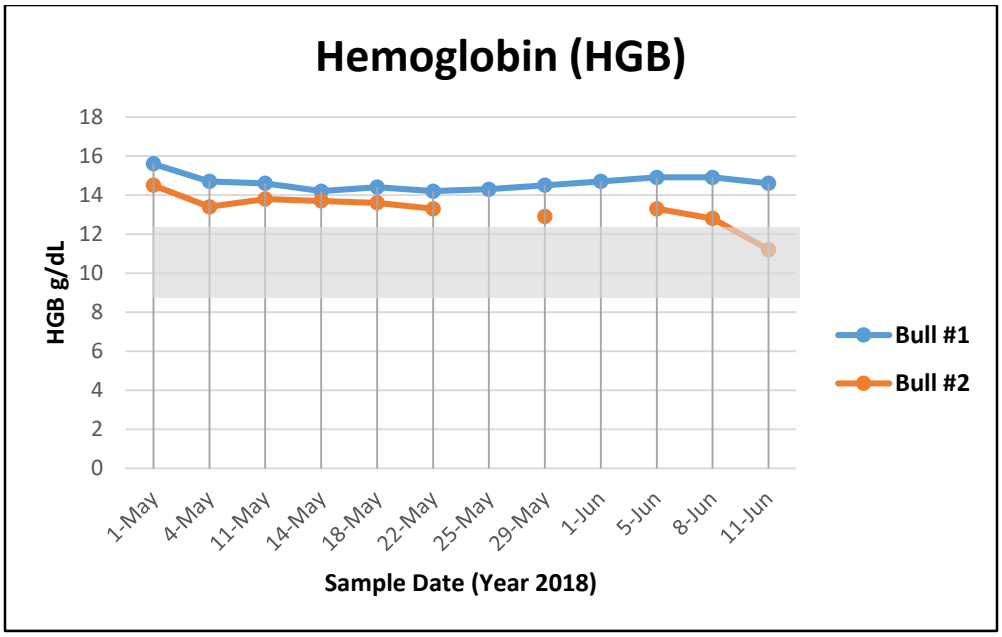

Figure 3.2 Results of hemoglobin concentration on CBC. Reference interval used is 8.7 – 12.4 g/dL, as indicated by gray box on graph (Cornell University, 2014). No sample was able to be obtained from bull #2 on 5/25 and 6/1.

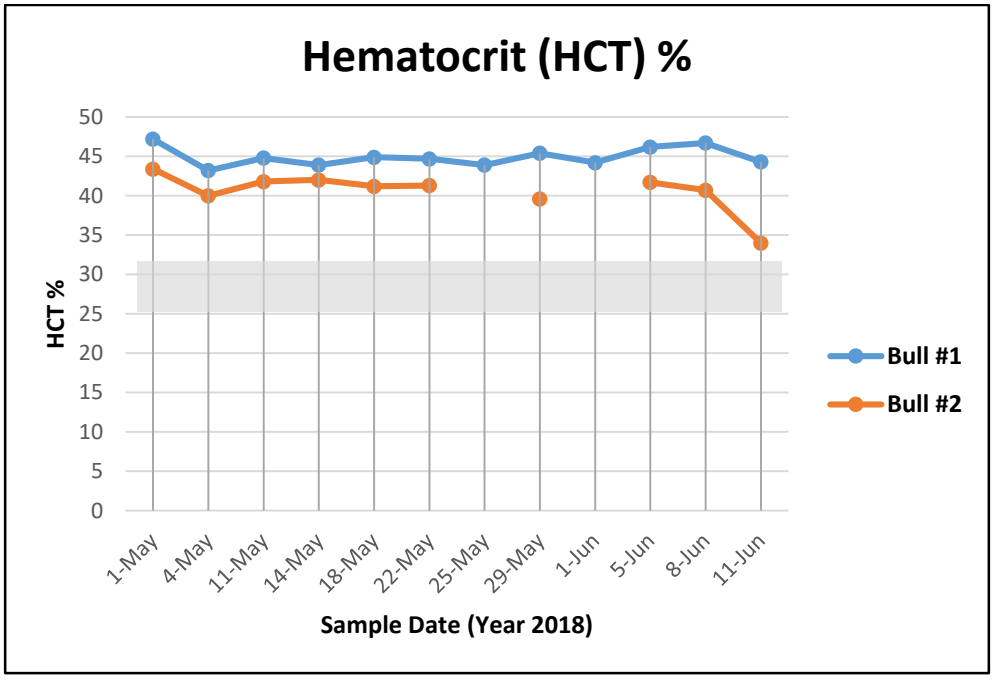

Figure 3.3 Results of hematocrit percentage on CBC. Reference interval used is 25 – 33%, as indicated by gray box on graph (Cornell University, 2014). No sample was able to be obtained from bull #2 on 5/25 and 6/1.

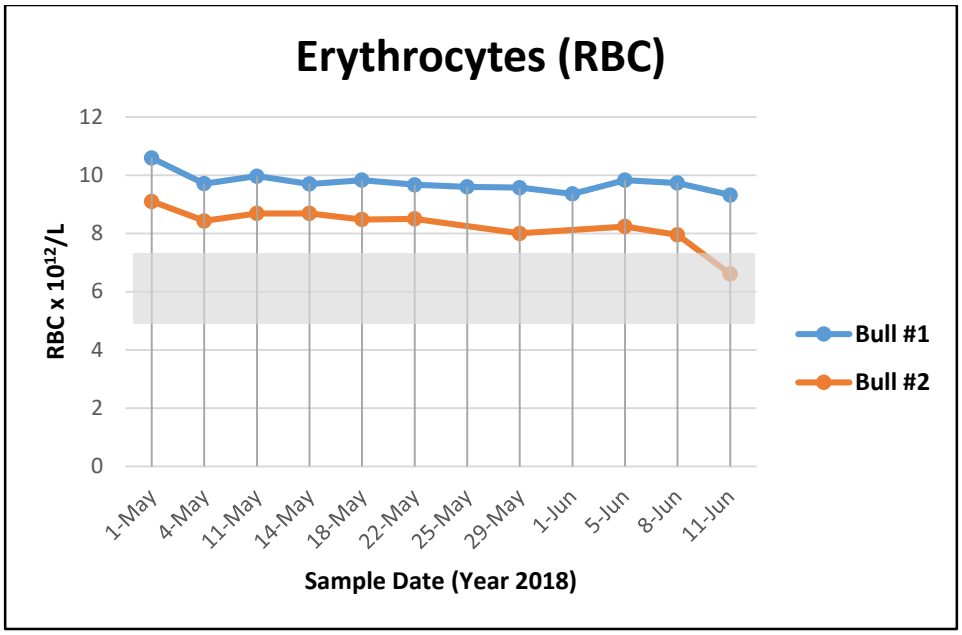

Figure 3.4 Results of erythrocyte count on CBC. Reference interval used is 5 – 7.2x10^{12}/L, as indicated by gray box on graph (Cornell University, 2014). No sample was able to be obtained from bull #2 on 5/25 and 6/1.

Figure 3.5 shows the results obtained from the i-STAT analyzer for blood lactate concentration. While great care was taken to ensure all blood samples were taken from an artery, an arterial sample was unable to be obtained in several samples. Distinction between which samples were arterial in origin and which were venous in origin is provided with the figure. For bull #2, complications arising from mild hematoma formation and bull behavior precluded blood sample collection for blood gas analysis on one of the scheduled sample days. The day on which a blood sample was unable to be obtained for bull #2 is noted in the figure. For measurement of lactate specifically, arterial or venous blood is appropriate for accurate interpretation of lactate concentration (Allen and Holm, 2008). The main blood gas parameter derangement noted was hyperlactatemia (Cornell University, 2014). All other blood gas parameters were within reference intervals during the study period.

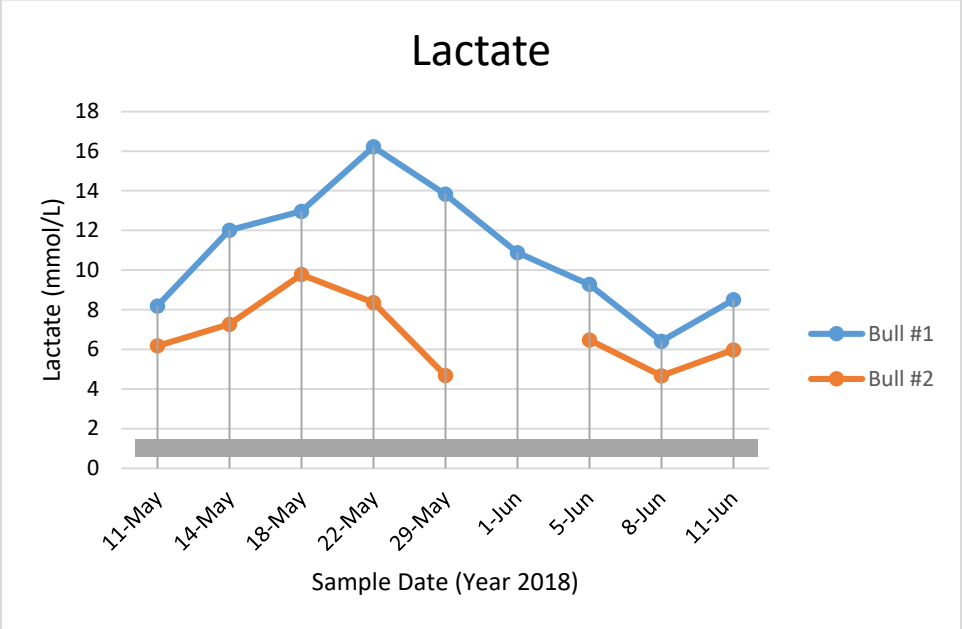

Figure 3.5 Lactate results as recorded by i-STAT. Reference interval used is 0.6-1.4 mMol/L, as indicated by gray box on graph (Cornell University, 2014). Auricular artery samples were obtained on 6/5 and 6/11 for Bull #1 and on 5/14and 6/11 for Bull #2. All other samples were venous. No sample was obtained from Bull #2 on 6/1. For both bulls, on 5/25 the i-STAT machine experienced excessive heat. As a result, data from that sample date was not included in this graph.

Figures 3.6-3.9 are photographs of the gross necropsy for each bull. Measurements for ventricular wall thickness, right ventricular length and width, and heart size are provided in the figures. The hearts of each bull were enlarged as shown in figure 3.8. Grossly, there is dilation of the right ventricle in both hearts. Figure 3.9 shows a transected view of the ventricles of each heart. The transected view of the heart from bull #2 shows that the muscular walls of both the right and left ventricles are similar in size. The thickness of the right ventricular wall for bull #2 was 1.7 cm. and the thickness of the left ventricular wall was 2.8 cm. However, the transected view for bull #1 shows the right ventricular wall to be 1.7 cm. thick and the left ventricular wall to be 3 cm. thick. Bull #2

also had a smaller product of length and width of the right ventricular chamber compared to bull #1 at 105 cm. for bull #2 and 130.95 cm. diameter for bull #1.

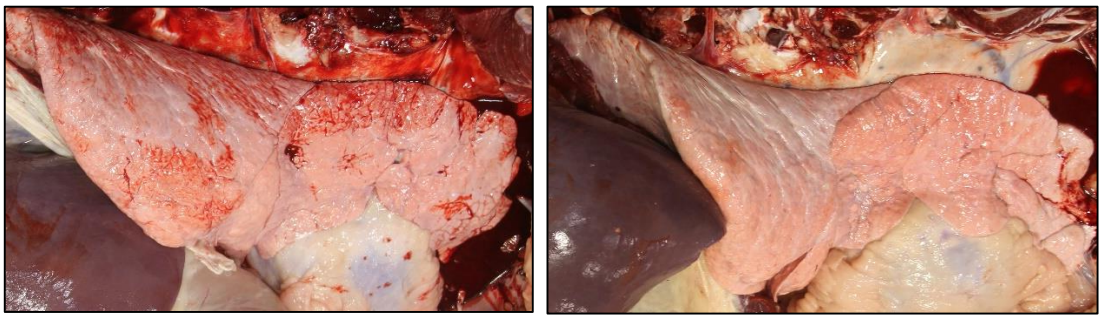

Figure 3.6 Right lung as seen with animal in left lateral recumbency. Bull #1 is on left and bull #2 is on right.

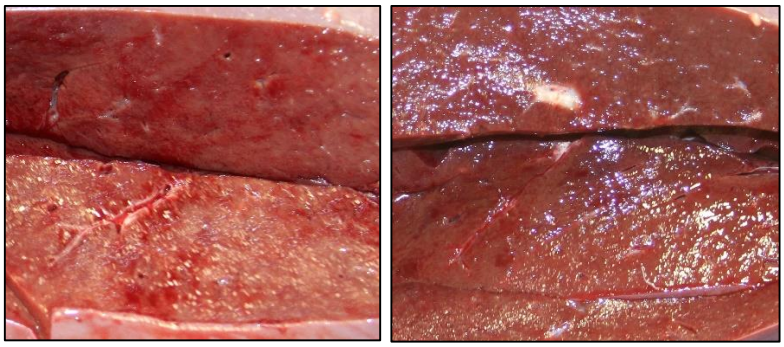

Figure 3.7 Livers of bull #1 (left) and bull #2 (right).

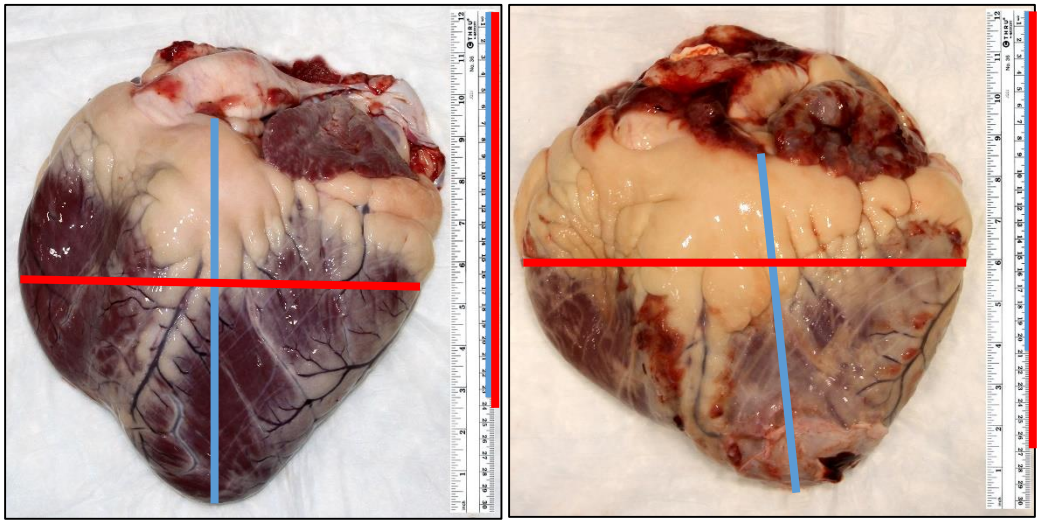

Figure 3.8 Hearts of bull #1 (left) and bull #2 (right). In each photo, the right ventricle is on the left side of the photo and the left ventricle is on the right. For bull #1, width was 24.1 cm (red line) and base to apex was 23.4 cm (blue line). For bull #2, width was 26.8 cm (red line) and base to apex was 20.8 cm (blue line).

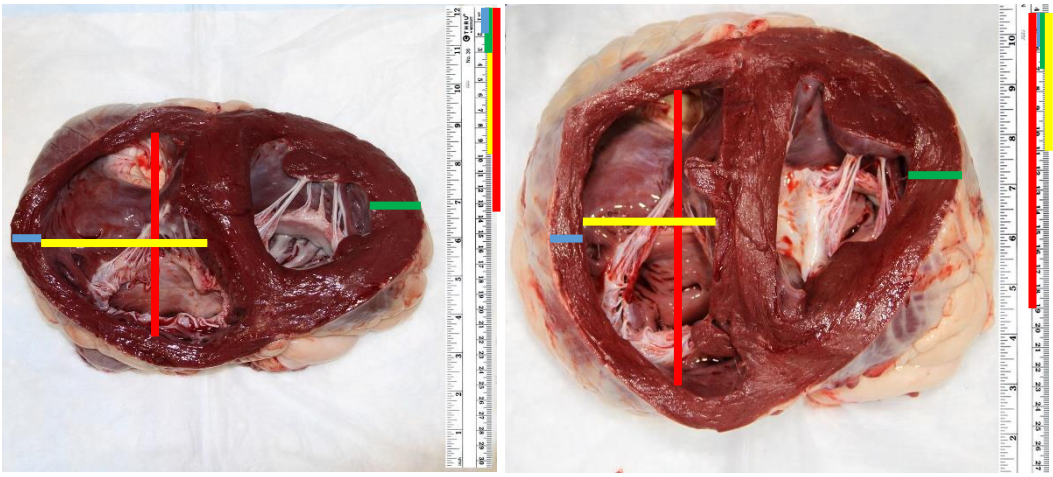

Figure 3.9 Transverse section of hearts from bull #1 (left) and bull #2 (right). In each photo, the right ventricle is on the left side of the photo and the left ventricle is on the right. For bull #1, right ventricular wall thickness was 1.7 cm (blue line), left ventricular wall thickness was 3 cm (green line), right ventricular chamber length was 13.5 cm (red line), and right ventricular chamber width was 7 cm (yellow line). The product of length and width for right ventricular chamber of bull #1 was 130.95 cm. For bull #2, right ventricular wall thickness was 1.7 cm (blue line), left ventricular wall thickness was 2.8 cm (green line), right ventricular chamber length was 15 cm (red line), and right ventricular chamber width was 7 cm (yellow line). The product of length and width for right ventricular chamber of bull #2 was 105 cm.

Discussion

The purpose of this report was to evaluate the physiological effects of moving 2 bulls affected with pulmonary hypertension from approximately 1219 m. elevation to approximately 518 m. elevation. There is evidence that hypoxia may be associated with BCHF development in feedlot cattle (Moxley et al., 2019). The pulmonary arterial hypertension diagnosed in both bulls prior to the beginning of this study may have been related to hypoxia. The persistent pulmonary arterial hypertension, erythrocytosis, and persistent hyperlactatemia noted in the bulls throughout the study period can all be

initiated by tissue hypoxia and therefore support the presence of tissue hypoxia in the bulls throughout the study period.

Pulmonary arterial pressures for both bulls in this case report generally declined over the observation period (table 3.0). The decline in pulmonary arterial pressure may show that decreased altitude and concurrent increased atmospheric oxygen concentration alleviated pulmonary arterial constriction and resulting pulmonary arterial hypertension that were initiated by systemic hypoxia. However, confounding variables that may have also caused the decrease in pulmonary arterial pressure are the change in diet and social structure experienced by the bulls. At the ranch of origin, the bulls were on a high energy diet. After removal to lower altitude, the bulls were on a less energy dense diet. The decrease in caloric intake may have decreased cellular energy intake and use, thereby alleviating some degree of tissue hypoxia. Also, at the ranch of origin, the bulls were in a pen with several other bulls. After moving to lower altitude, the bulls were kept in a pen together, with no other animals in the pen with them. Therefore, this change in social structure may have decreased the demand for oxygen by decreasing the need to compete for feed, water, and social rank.

Hematological and blood gas parameters are presented in figures 3.0-3.5. Hematological parameters (fig. 3.0-3.4) measured on CBC were within published reference intervals with the exception of mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), hemoglobin (Hgb), hematocrit (HCT), and erythrocytes (RBC) (Cornell University, 2014).

The blood gas data are observations based on the samples that were available. The majority of available samples for this report were venous samples, as specified in the

figure. Two studies, one conducted on dogs and the other on horses, have shown that both arterial and venous blood may be appropriate for blood gas analysis (Ilkiw et al., 1991; Speirs, 1980). For measurement of lactate specifically, arterial or venous blood is appropriate for accurate interpretation of lactate concentration (Allen and Holm, 2008). The main blood gas parameter derangement noted was hyperlactatemia (fig. 3.5) (Cornell University, 2014). All other blood gas parameters were within reference intervals during the study period.

Elevations of RBC, HCT, and HgB values are indicative of erythrocytosis. Erythrocytosis can result from increased erythropoietin production in response to tissue hypoxia. The upregulated erythrocytic production also would increase concentrations of immature erythrocytes in the blood, leading to the decreased MCHC and increased RDW that was noted. The upregulated erythrocytic production culminating in erythrocytosis indicates the bulls may have been experiencing some level of tissue hypoxia during the study period.

Another indication the bulls were experiencing tissue hypoxia is that blood lactate concentration was consistently elevated throughout the study period. In states of tissue hypoxia, anaerobic respiration occurs, leading to lactate production as the end product of glycolysis (Allen and Holm, 2008; Madias et al., 1986; Pang and Boysena, 2007).

Gross necropsy, shown in figures 3.6-3.9, demonstrated the typical findings in animals with pulmonary hypertension (Reef and McGuirk, 2015). Figure 3.7 shows the livers of each bull. Animals in fulminant BCHF will have very congested livers with rounded edges and cross section of BCHF affected livers will show the characteristic

"nutmeg" appearance (Moxley et al., 2019). No visual evidence of these lesions was noted in the livers of these 2 bulls.

The hearts of each bull were enlarged as shown in figures 3.8 and 3.9. Two studies reporting ventricular diameter (Braun and Schweizer, 2001) and ventricular wall thickness (Buntyn et al., 2017) in healthy cattle were used for comparison. Using 2-D mode echocardiography, Braun and Schweizer measured the diameter of the left and right ventricles of 51 healthy adult cows. They found the diastolic diameter of the right ventricle in the caudal long axis was ~ 4.1 cm. The caudal long axis diameter measurements for the bulls in this study was 13.5 cm for bull #1 and 15 cm for bull #2. Ventricular wall thickness was measured by Buntyn et al. (2017) in 20 feedlot heifers during a clinical trial evaluating the impact of zilpaterol hydrochloride administration on blood chemistry parameters and internal organ weight and morphology (Buntyn et al., 2017). Their measurements were 3.54 cm for both the control and zilpaterol supplemented groups for left ventricular free wall thickness and 2.11 cm in the control group and 1.99 cm in the zilpaterol supplemented group for right ventricular free wall thickness. Ventricular wall thickness for both bulls in this study was smaller than the thicknesses measured by Buntyn et al. (2017). Therefore, the enlargement noted at necropsy of the bulls in this study is likely due to dilatation of the ventricles.

Cardiac enlargement is typical in animals affected by pulmonary hypertension and/or BCHF. Cardiac enlargement in the bulls discussed in this report suggests that while clinical signs of BCHF were not detectable at the time of euthanasia, cardiac pathology resulting from pulmonary hypertension was progressing.

One of the limitations of this report is that no control animals were included because the cost of obtaining appropriate animals (e.g. reproductive age, yearling bulls) was impractical given the industry demand for such animals. The 2 bulls were intended for use in the breeding herd at the ranch of origin. Having control animals would have helped prevent the introduction of bias in the interpretation of the results by helping to control for any confounding variables, such as diet change and change in social structure, that may have affected the results noted in the 2 bulls. This could have been accomplished by selecting appropriate control animals to experience the same changes in altitude, diet, and social structure subjected to the 2 study subjects.

The objective of this case study of 2 bulls previously diagnosed with pulmonary arterial hypertension was to observe the hemodynamic and hematologic effects of moving them from approximately 1219 m. to approximately 518 m. The results of this study show that moving cattle with pulmonary arterial hypertension from moderate altitude to lower altitudes leads to a reduction in pulmonary arterial pressure, but tissue hypoxia may persist for a longer period of time than pulmonary arterial hypertension. Currently, feedlot producers have few options for managing cattle affected with pulmonary arterial hypertension. This report fails to reject the hypothesis that relocating affected animals to areas of lower altitude may be an effective management strategy. Further research that includes negative control animals should be done to determine if the hemodynamic and hematologic effects seen in this report can be replicated.

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Sources and Manufacturers

EDTA blood collection tubes (Medtronic, Minneapolis, MN)

Serum separation gel tubes (Medtronic, Minneapolis, MN)

Tempus Blood RNA Tube (Grenier Bio-One, Kremsmünster, AT)

Heparinized syringe (Sanguis Counting Kontrollblutherstellungs, Nümbrecht, DE)

iSTAT handheld blood analyzer and CG4+ cartridge (Abbott Point of Care Inc., Princeton, NJ)

BM5 Patient Monitor (Bionet Co., Seoul, KR)

Element HT5 Veterinary Hematology Analyzer (Heska, Loveland, CO)

Declaration of conflicting interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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CHAPTER 4: CONCLUSION

Bovine congestive heart failure (BCHF) is a condition that poses a great challenge to the beef industry. Evidence presented in this thesis is consistent with previous evidence supporting an increase in frequency of BCHF since its initial documentation in the 1970s (Jensen et al., 1976; Neary et al., 2016). Currently, there are many knowledge gaps regarding BCHF, but the present thesis will aid in filling these knowledge gaps by increasing the body of data regarding BCHF case frequency and timing and providing evidence for one possible management strategy involving transporting affected animals from higher altitude to lower altitude.

The purpose of the epidemiologic study in this thesis was to characterize the frequency and timing of BCHF in feedlot cattle in order to provide a means to elucidate the sequence of events that culminates in clinical disease and in understanding the etiology of the disease. Data in that study fails to reject the hypothesis that BCHF case incidence has increased over the six-year study period at one feedlot. The increase in incidence of BCHF cases may have been related to increases in number of cattle fed or time at risk at this feedlot. However, the cases/100,000 head days was presented in this study to account for this possibility. Even after this normalization was done, a general increase over the six-year study period was noted. Also, evidence presented in this study shows that BCHF cases develop at all stages during the feeding period, primarily midway through the feeding period. Therefore, this study rejected the hypothesis that BCHF is exclusive to late-fed or fat cattle. Characterization of the timing and frequency of incident BCHF cases will contribute to understanding the mechanism of disease by providing information about the sequence of disease timing.

This thesis also fails to reject one particular management strategy that can be used to mitigate BCHF. The case report in this thesis shows that removing two bulls affected by pulmonary arterial hypertension from the ranch of origin at 1219 m. elevation and bringing them to a lower elevation resulted in reduced pulmonary arterial pressure. However, there are confounding variables that may have affected the bulls' oxygen status. As part of the move to lower elevation, the bulls diet and social structure also changed. At the ranch of origin, the bulls were on a high energy diet. After removal to lower altitude, the bulls were on a less energy dense diet compared to their previous diet. The decrease in caloric intake may have decreased cellular energy intake and use, thereby correcting the overall oxygen status of the bulls. Also, the social structure of the bulls changed after the move. At the ranch of origin, the bulls were in a pen with several other bulls. After moving to lower altitude, the bulls were kept in a pen together, with no other animals in the pen with them. Therefore, this change in social structure may have decreased the bodily demand for oxygen by decreasing the need to compete for things such as feed or water.

Despite these confounding variables, data from this case report provides insight into the different hemodynamic and hematologic changes that may occur after removal to lower altitude. This data will be useful for further research investigating pulmonary arterial hypertension and BCHF that occurs at moderate altitude (335 – 1524 m.) and for development of management or therapeutic modalities for BCHF.

Each of the studies discussed in this thesis provide information that helps fill two important gaps in existing knowledge of the frequency and timing of BCHF as well as gaps in knowledge of mitigation strategies to decrease the impact of BCHF. Filling these

gaps will aid in characterization of the underlying mechanism of disease by providing data regarding the onset of BCHF cases and when the various pathologic changes develop during the course of disease. Data from both of the studies reported in this thesis deepen our understanding of BCHF, bringing us closer to finding a solution to the BCHF problem.

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