ABSTRACT

RAJO GOMEZ, EDWIN BENJAMIN. Evaluation of the Effects of Endophyte-Infected Tall Fescue Consumption on the Pulmonary Arterial Pressure of Beef Cattle. (Under the direction of Daniel H. Poole).

Tall fescue (*Schedonorus arundinaceus* [Schreb.] Dumort) is the principal forage utilized by cattle producers in the Southeastern U.S. Among the different varieties of tall fescue used in this region, many have the peculiarity of sharing a symbiotic relationship with an endophytic fungus (*Epichloë coenophiala*), which is known to produce different ergot alkaloids that support the plant performance. The benefits obtained by the plant include an increased resistance to drought, pest attacks, and poor edaphic conditions, in addition to greater forage productivity and tolerance to high animal stocking rates. However, the ergot alkaloids produced by endophyte-infected varieties of tall fescue are detrimental to cattle, as they induce different negative responses that are commonly referred to as fescue toxicosis. These effects include decreased animal performance, suppressed hormone production, poor reproductive efficiency, reduced calf growth, retained winter hair coats, increased heat stress and blood vessel vasoconstriction. Considering these negative consequences, different efforts have been made to identify and develop management strategies that can aid to reduce these effects and increase overall productivity and efficiency in cattle operations. Among these methods, the identification of tolerant animals within populations following chronic exposure to strenuous conditions has proven to be a viable option, through the use of phenotypic selection parameters and expected progeny differences (EPD) in the genetic management of the cattle herd. EPDs are commonly used in cattle operations to identify tolerance to specific diseases, such as high-altitude disease. This condition is experienced by cattle in regions of high altitude where oxygen concentrations in the air are reduced. This lack of oxygen causes pulmonary arterial vasoconstriction, which

changes the normal blood flow pattern and adds stress to the cardiovascular system that can result in right-side cardiac failure and death of the animal in severe cases. Susceptible animals to high-altitude disease will tend to show increased mean PAP values (>44 mmHg), whereas tolerant animals will report normal mean PAP values (<44 mmHg) in spite of the reduced oxygen concentration in the air. The similarities found in vascular vasoconstriction between high-altitude disease and fescue toxicosis support the hypothesis that the consumption of ergot alkaloids present in endophyte-infected tall fescue could have an increasing effect on the pulmonary arterial pressure (PAP), and that it could be utilized as a phenotypic test to identify animals with an increased fescue tolerance, facilitating the implementation of the PAP EPD to potentially predict any genetic differences that can aid in identifying cattle with a lower risk of developing fescue toxicosis following exposure to the ergot alkaloids. Therefore, the objective of this study was to examine the relationship between PAP, hematologic measurements, and common production parameters in cows grazing endophyte-infected fescue, as a means to identify animals that are highly susceptible or resistant to fescue toxicosis. This study was conducted at Upper Piedmont Research Station (UPRS) and Butner Beef Cattle Field and Laboratory (BBCFL) in North Carolina. Pregnant purebred Angus cows in an age range between two and three years at UPRS grazed at endophyte-infected tall fescue pastures exclusively, whereas pregnant purebred Angus cows in an age range between two four years at BBCFL were randomly divided to graze either endophyte-infected (EI) or novel-endophyte (EN) tall fescue pastures for 14 consecutive weeks. PAP measurements were realized every four weeks. Overall, UPRS cows had significantly lower ($P<0.0001$) mean PAP values than both BBCFL groups, whereas the BBCFL (EI) cows had lower mean PAP values than the BBCFL (EN) cows. Hematocrit differences were observed between groups ($P<0.0001$), where UPRS cows had

higher hematocrit percentages than both BBCFL groups. Differences were also observed in performance parameters, where UPRS cows had significantly higher body weights (P<0.0001) than both BBCFL groups, but the BBCFL (EN) tended to have higher average daily weight gains (ADG) (P=0.0576) than the BBCFL (EI) and UPRS cows throughout the study. In addition, differences were observed (P<0.0001) in body condition scores (BCS), where UPRS cows had higher BCS than both BBCFL groups of cows. Rectal temperatures also reported significant differences (P<0.0001), where UPRS cows had higher rectal temperatures than both BBCFL groups. Additionally, BBCFL (EN) cows had significantly lower (P=0.0006) hair coat scores (HCS) and lower (P=0.0026) hair shedding scores (HSS) than UPRS and BBCFL (EI) cows. Comparably, BBCFL (EN) cows also had significantly higher (P<0.0001) progesterone (P4) concentrations than BBCFL (EI) and UPRS cows throughout the study. Contrary to the established hypothesis, consumption of endophyte-infected tall fescue caused a reduction in the mean PAP values of cows. Additionally, the differences observed in hematocrit indicate a potential interaction with ergot alkaloids. Further, exposure to endophyte-infected tall fescue had negative effects on the evaluated physiological and performance parameters. Based on these results, a novel approach to evaluate the impact of endophyte-infected tall fescue consumption on PAP is established. Nonetheless, further studies are necessary to determine if PAP can be implemented as a phenotypic test to identify tolerance to fescue toxicosis in beef cattle.

Evaluation of the Effects of Endophyte-Infected Tall Fescue Consumption on the Pulmonary Arterial Pressure of Beef Cattle

by

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DEDICATION

This thesis is dedicated to God Almighty, for His immeasurable kindness and love, and to many incredibly important people in my life that have always supported my dreams. To my wife Carolina, for being my perfect partner and my biggest source of strength. This thesis and degree would have not been possible without you by my side. To my two wonderful sons, Benjamin Andres and Martin Eduardo, for being my biggest source of motivation to become a better man to serve as your role model. To my parents, for your permanent love and all the sacrifices you did for me and my siblings to facilitate our access to high-quality education as we grew up, and for the constant support you both have given me and my family during this adventure. To my wife's parents, who have become my parents as well, for permanently supporting and caring for me and my family. This thesis is dedicated to you all.

BIOGRAPHY

Edwin Benjamin Rajo Gomez was born in Siguatepeque, a small town located in the central region of Honduras, Central America, where he lived with his father, Edwin Rajo, mother, Rosaura Gomez, and siblings Lindelly and Eduardo Rajo Gomez. Benjamin was raised in an agricultural environment, as his mother has a small farm where she produces coffee, beans, and citrus fruit, and his Grandfather Benjamin owns a larger farm where he produces cattle, coffee, avocado and hardwood trees. Evidently, this exposure led Benjamin to become more interested in agriculture and motivated him to pursue a Bachelor's degree in Agricultural Sciences from Zamorano Panamerican Agricultural University, which he began in January of 2009.

Following the obtention of his degree, Benjamin worked as a farm manager for nine years in the northern region of Honduras. The different challenges faced motivated him to develop research modules inside the farm, with the objective of increasing forage productivity utilizing a silvopasture model, evaluating different diet results on crossbred steers and heifers, and reducing mortality rates during calving season. The positive results obtained motivated him to resume his academic career and apply to Graduate school. In the fall of 2021, Benjamin started his Master's degree at North Carolina State University, focusing on studying the impact of fescue toxicosis on beef cattle physiology, but also collaborating on other projects related to ruminant production. Upon the completion of his Master's degree, Benjamin will continue his studies at North Carolina State University to pursue a Ph.D. degree in Animal Science.

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CHAPTER 1

Literature Review

Beef Cattle Production in the United States

For the past 6,500 years, cattle have had substantial importance to humans as a source of meat, milk, textiles, objects of worship, and labor. As the human race evolved, it transitioned from hunting wild bovids to domestication of some species, which facilitated a more steady and accessible supply of the previously mentioned items (Wilson et al., 1965). In 1493, Cristopher Columbus introduced domesticated cattle to the American continent for the first time. From that year on and until 1512, multiple imports of cattle from Europe and Africa took place, which instigated the dispersion of cattle throughout North and South America (McTavish et al., 2013). From the animals originally brought by the different explorers to the American continent, three major strains were produced: the wild cattle of the Caribbean islands, the fighting bulls of Mexico, and the Longhorns of the American plains. Later on, the first lot of British cattle was brought in to the Jamestown Colony of Virginia in 1611 (Wilson et al., 1965). Subsequent to this period, many other cattle breeds were imported to the American continent with the objective of identifying productive individuals that could adapt appropriately to the environment and provide advantages over the already established genetic lines. The first recognized modern breed that was imported to the United States was the Shorthorn in 1793. The following foreign breeds to be introduced were the Hereford in 1817, and the Aberdeen Angus in 1873, among several others (Herring, 2014). Relating to the United States cattle industry, the import of these breeds throughout its history has played a fundamental role in increasing cattle productivity and quality, positioning the country as one of the major beef producers and industry leaders in the world.

In economic terms, beef cattle production represents one of the most important agricultural commodities in the United States, providing an input of around 17 percent of the $462 billion in total cash receipts of the annual agricultural production (USDA-ERS, 2022b).

Operationally, the beef industry of the United States can be categorized into the following segments: cow-calf, stocker, feedlot, packer, retailer and consumer (Herring, 2014). Over 40% of the territory in the United States is used for activities related to beef production systems, which are mainly pasture-based for cow-calf and stocker enterprises found in all 50 states. Feedlot establishments are concentrated in the central region of the country due to their proximity to different crop and by-products sources that provide the necessary ingredients to formulate high energy and protein concentrate-based diets (Greenwood, 2021). In July 2022, a total of 98.8 million head of cattle and calves nationwide was estimated, of which 34.6 million are beef cows and calves (USDA-NASS, 2022). Around 55% of the total beef cows are also found in the Central states, due to the extensive grasslands and plains that can be used for cattle grazing. Approximately 20% of the national cow herd is established in the Western region, and an additional 20% is located in the Southeastern region. The remaining 5% of the beef cows are dispersed all through the Northeastern states, Hawaii and Alaska (Drouillard, 2018).

Beef Cattle Production in the Southeast United States

The Southeast region of the United States is distinguished by its diversity in terms of climate and natural ecosystems, including variable temperature, precipitation, topography and edaphic distributions that provide optimal conditions for agricultural production. The total land area of the Southeast is estimated to be 135 million ha, which represent a 14.9% of the United States' territory. From this amount, around 11 million ha are used as grassland pastures for grazing species, which constitute 4.5% of the national grassland area (Ingram et al., 2013). In terms of productivity, it was estimated in 2016 that the Southeast beef industry generated over $13.4 billion in gross sales, from which $4.3 billion correspond to on-farm production of beef cattle (English et al., 2020).

The principal type of cattle operation found in the Southeast United States is the cow-calf operations, which usually are small productive units that depend on improved pastures (Drouillard, 2018). The most recent census of agriculture estimates the average cow herd is 44 head. Frequently, operations that own 50 head or less are either a part of a larger corporate system, or are a secondary source of income and resources to their owners (USDA-ERS, 2022a). Some of the characteristics that facilitate this type of cattle operation in the region are the possibility of grazing for longer periods due to the warmer environmental temperatures throughout the year, which lead to a reduction in the requirements of winter supplementation feed. Additionally, some of the topography found in this part of the country is not suitable for crop production, but is favorable for the establishment of pasturelands (Herring, 2014).

The primary product of this type of operation is weaned calves. A portion of the heifer calves weaned that possess superior traits and desired phenotypes are selected for replacement females and will be kept in the herd. The remaining female and male weaned calves usually follow one of two trajectories. The largest amount, estimated to be about 60%, of calves are sold to stocker or backgrounding operations to be raised on grazing or forage-based diets until they reach a year or more of age, which gives them the denomination of “yearlings”, before heading to the feedlots to be finished with high-energy concentrate diets. The other 40% of calves are known as “calf-feds” due to their direct transition to feedlots following the weaning phase (Drouillard, 2018).

Furthermore, the cow-calf operation can also be divided into seedstock and commercial categories, depending on the genetic value of the cattle they raise. The seedstock branch focuses on raising purebred animals, and are commonly registered with a specific breed association. These establishments keep updated and detailed records of their cattle’s pedigree and performance, which are valuable assets to their main purpose of selling breeding animals, most distinctly bulls, to commercial producers. The commercial cow-calf operation consists of producing animals of lower genetic merit (usually crossbred cattle), but possessing increased heterosis that benefits the productive traits that are favorable for beef production. There are a greater number of commercial establishments than seedstock operations. However, it is also common that seedstock owners also have a commercial component in their farms (Herring, 2014).

Genetic selection parameters within the Cow-Calf Operations

Within the beef cattle industry, genetic management decisions have a substantial influence on parameters that impact the efficiency and profitability of the herd. These decisions must be part of a well-defined and consistent genetic improvement plan that takes into account replacement female selection, sire selection to produce these replacement individuals, and appropriate selection of the sires that will be bred to these replacement heifers, as these parameters will determine the genetic pool of the herd in the future (Grings and Wright, 2020). Additionally, this strategy must also focus on improving deficiencies found in the herd, especially those that are considered as culling characteristics. Some of the traits of interest used by producers to influence productivity and efficiency include, but are not limited to, maternal ability, birth weight, mature weight, growth rate, feed efficiency and reproductive performance (Kutz, 2023). One of the most powerful tools available for trait selection is the use of genetic prediction, commonly referred to as Expected Progeny Differences (EPD’s). An EPD predicts the genetic value and expected performance of an individual’s progeny. These values are calculated based on performance records of the individual and its relatives. The number of records used in these calculations will have a direct proportionate impact on the selection accuracy of the individual, meaning that higher accuracy values will reduce the selection risk and increase the confidence on the individual's genetic merit. The accuracy of the EPD can be increased by using a substantial number of performance records that are provided by reliable sources, such as breed organizations (Gonda, 2020). The progress in genomics, precise parentage estimates, and data interpretation have all provided the beef cattle industry a revolutionary platform through the use of EPDs to improve genetics in the herd in a more rapid and efficient manner that consequently increases the profitability within the operation. Most of the beef cattle breed associations registered in the United States have incorporated DNA testing and genomic analyses into their methodologies to provide an enhanced and detailed portfolio to their clientele (Bryant, 2019).

Relevant breeds and their impact in Cow-Calf Operations

Producers usually consider different environmental, economic, and management factors at the moment of deciding which breed(s) is most appropriate for their operation. Three major biological groups of cattle can be found within the United States, which have been classified depending on their respective area of origin. The continental European breeds are considered highly productive animals, considering their ability to rapidly increase their body weight and develop carcasses with hefty, lean muscularity. Simmental, Limousin, Gelbvieh and Charolais cattle all belong to this group and have an important presence in commercial cow-calf operations that utilize crossbreeding strategies. In addition, the American breeds, which are commonly found in the Southeastern region, are composite animals that were developed in the United States from imported Asian Zebu (*Bos indicus*) cattle. Among this group, the most important breeds are the Brahman, Brangus, Santa Gertrudis, and Beefmaster. Some of the relevant traits found in these cattle are longevity, high tolerance to parasites and heat, and their capability to thrive on low-quality grazing conditions. Furthermore, the British beef breeds tend to have smaller frames, but are widely known for their ability to deposit and retain intramuscular fat, which substantially increases the carcass quality and economic value. Additionally, British breeds reach puberty at an early age and have increased fertility and longevity. Hereford and Shorthorn are relevant breeds within this group. However, the Angus breed excels in popularity over the rest and is considered to have the greatest influence and dominance on the beef industry of the United States (Herring, 2014).

The Aberdeen-Angus breed, as its name declares, was founded in the counties of Angus and Aberdeen in the northeastern part of Scotland. It has been revealed by historians that in the early 16th century, two strains of polled cattle were used as parental genetic lines to form the breed (Angus Cattle - OSU, 2021). Further on, the first recorded importation of the breed to the American continent took place in Canada in 1859, and was made by Sir George Thompson, Governor of the Hudson Bay Company. Since no progeny was recorded, the recognition of the first productive lot was given to Professor Wm. Brown at the Ontario Experimental Farm located in Guelph, Ontario. Following imports of Angus cattle to Canadian territory took place between 1860 and 1882 (Canadian Angus Association, n.d.). In 1873, George Grant imported the first four Angus bulls from Scotland to Kansas, marking the foundational establishment of the breed in the United States. Considering Shorthorn was the dominant breed at that time, cattlemen initially had difficulties integrating Angus cattle to their herds due to their firm black color and polled heads. Disregarding the negative opinions, Grant continued his work and crossed his bulls with native Texas longhorn cows, generating several crossbred black, polled calves that outperformed during the cold winter months, and had superior weights in the following spring. Following this successful trial, several imports between 1878 and 1883 brought an estimate of twelve hundred cattle from Scottish lands to the Midwestern United States, securing the permanency of the Angus breed in the North American cattle industry (American Angus Association, n.d.). The American Angus Association (AAA) was founded in 1883 with the mission of serving as the breed's registry. Nowadays, AAA is considered to be the industry-leading beef organization, with thousands of members that usher an expansive network devoted to the progress of the beef industry (Angus: The Business Breed, n.d.).

There are multiple reasons that have led cattle producers to incorporate Angus genetics into their herds. Angus cows are known to possess desired traits in a female, such as reaching puberty at an early age, high fertility and short gestation periods, low birth weights and advantageous calving ease, considerable milk production and a strong maternal instinct. Angus calves offer an efficient growth and development, shortening the time to reach the weaning phase. In beef productivity terms, the breed excels in the ability to produce a high-quality carcass, with a superior marbling that increases the final cuts' desirability and value (Angus Advantages, n.d.). These advantageous attributes have increased the demand of the breed, leading to the origin of a premium in cattle markets assigned to black hided individuals, as a synonym of being carriers of the Angus genetics. Consequently, the number of producers raising Angus cattle has experienced an exponential increase, which has led to a superlative support to develop a robust system of resources, especially in the area of genetic improvement. The American Angus Association has the largest beef cattle registry in the United States, which has periodically received records from certified producers since 1958. Those records, in conjunction with ancestral data, DNA and performance statistics, are used for genetic assessment and develop genomic-enhanced EPDs, which allow producers the ability to evaluate and compare individuals in the database and make decisions to improve the genetics in their respective herd

(Angus Advantages, n.d.). As a result, it is estimated that 70% of the beef cow herds in the United States are covered by Angus bulls. In addition, an increase has been noted in average marbling scores, with 6.26% of all U.S fed cattle receiving a Prime stamp in the USDA carcass grading scale in 2016, compared to less than 2% of cattle qualifying for this degree in 1995 (Reiman, 2017). Undoubtedly, the Angus breed has had a tremendous impact since it was introduced to the United States, and has greatly influenced and endorsed the growth and development of its beef cattle industry.

Forage Management and Grazing Systems in the Southeastern U.S.A.

Forage systems represent one of the principal feed sources for cattle enterprises in the United States. The amount of forage availability and its nutritional value will depend on different parameters, such as the species used, plant maturity, management strategies and environmental conditions. Until 2012, the USDA-ERS estimated that over 10 million acres of land were designated for grazing lands in the Southeast region of the United States. Annual grazing systems are commonly found in this area, due to the extended mild temperatures and considerable rainfall found in this area throughout the year. In addition, these forages provide farmers with the opportunity to combine cattle production with certain row crops in the same operation (Leanne Dillard et al., 2018). Consequently, most of the cow-calf operations established in this region use pastures as the main feed source to provide an appropriate nutrition to the herd and maintain productive levels. Pasture management for grazing cattle implies understanding and analyzing the interface between two species, where the selected forages need to be maintained under the appropriate conditions in order to provide beneficial nutrition to the herd. Considering all the external variables that affect this model, different strategies must be considered to form a productive, efficient, and sustainable system (Evers, 2008). Cattle producers in the Southeast have developed several grazing techniques, taking into account each of the peculiarities found in their locations. Some of the grazing methods that are commonly used are continuous, rotational, creep, and strip grazing. From these methods, strip and rotational grazing both offer an improved utilization of the pastures, hence increasing the quantity and quality of forage that is produced (Grazing Methods, n.d.). Producers also rely on seasonal forages, as most of the herbages utilized in this region can be classified into warm-season and cool-season species, based on their respective growth cycles throughout the year. Warm-season perennial forages are used during the late-spring and summer months due to their high yields and drought tolerance, in spite of their more fibrous and less digestible nutritional values (Harmon et al., 2019). These herbages are also combined with row crop rotations as an alternative to combat disease and weed presence in the production lot (Leanne Dillard et al., 2018). Cool-season forages spread their production cycle into a bimodal distribution, with the first peak of production beginning simultaneously with the spring season, then dropping to a hiatus during the warmer temperatures of the summer, to follow the second production peak that begins in the fall and lasts until the beginning of the winter. Both cool-season grasses and legumes produce forage of high nutritional value, and are best utilized for animals with an increased nutrient demand (Evers, 2008). Among the different forages used in the Southeast, tall fescue (*Schedonorus arundinaceus* [Schreb.] Dumort) predominates in most grazing livestock operations (Allen at al., 1996).

Endophyte-Infected Tall Fescue

Tall fescue (*Schedonorus arundinaceus* [Schreb.] Dumort) is a widely grown cool-season perennial forage that is used in livestock production. It is highly valued in beef grazing operations due to its remarkable biomass production, tolerance to increased stocking rates, and persistence in diverse soil conditions. Tall fescue can be found in different regions of the United States, including small portions of the Pacific Northwest and lower Midwest, and an extensive area in the Southeast (Ball et al., 1993), and is estimated to cover more than 15 million hectares of grassland in the country (Alfaro and Moisá, 2022). As a cool-season forage, its growth periods concentrate in the spring and late fall months, when temperatures range between 4 and 25 degrees Celsius. Low pasture production during the extreme temperatures of summer, which limit both the quantity and quality of the forage, typically will be insufficient to meet the animal nutritional requirements (Roberts et al., 2015). Native to the European continent, tall fescue was first introduced to the United States in the 19th century but was not extensively planted until 1940 (Fribourg et al., 2009). In 1931, E.N. Fergus from the University of Kentucky decided to evaluate a particularly robust and flourishing variety, which was later released as the Kentucky-31 cultivar in 1943. This new tall fescue strain was better adapted to poor edaphic conditions, had a broader productive period, and increased pest and drought tolerances (Ball et al., 1993). These traits favored its rapid adoption and establishment in pastures across the country, despite the fact it was not officially certified as a cultivar until 1972 (Fergus and Buckner, 1972), and positioned it as one of the principal forages used for livestock grazing in the United States (Alfaro and Moisá, 2022).

In the 1960s, alkaloid compounds found in analyzed samples of the grass were linked to reports of animal disorders that had similarities to ergotism, a disease caused by consumption of grains infected with ergot alkaloids produced by the *Claviceps* fungi. It was until the mid-1970s, following a considerable number of analyses, that the endophyte infection in tall fescue was identified (Ball et al., 1993). Bacon et al. (1977) suggested that *Epichloë typhina*, a clavicipitaceous systemic endophyte, could be responsible for producing the alkaloids that caused the toxicosis syndrome. Bush et al. (1979) published several theories after analyzing samples of tall fescue, including as probable causal agents the loline, perloline and perlolidine alkaloids, in addition to other ergot and ergot-like vasoconstrictor alkaloids. Following these studies, Morgan-Jones and Gams (1982) reclassified the endophyte fungus into a separate and unique section, due to its singular taxonomy, and changed its scientific name to *Acremonium coenophialum*. Moreover, in lieu of genus reclassification following phylogenetic studies, the genus *Acremonium* was renamed as *Neotyphodium coenophialum* (Glenn et al., 1996). Lastly, in accordance to changes in international nomenclature rules for fungi that stated a single name to be used for each species, the genus *Neotyphodium* was annexed to the *Epichloë* genus, defining the current scientific name of the tall fescue endophyte as *Epichloë coenophiala* (Leuchtmann et al., 2014).

It is estimated that the symbiotic relationship between the endophyte and tall fescue forage can be found in 90% of the tall fescue pastures established in the United States, which has been proven to provide several benefits for both species (Chai et al., 2020). *E. coenophiala* is known to have a subtle mode of asexual reproduction, where instead of using spores as other fungi, it disseminates the next generation through seed-borne inoculation (Tsai et al., 1994). From the perspective of the endophytic fungus, the tall fescue plant offers an appropriate and safe environment to grow, develop and reproduce, assuring the completion of its life cycle. First, the seeds of tall fescue serve as an effective vehicle that stores and transports the mycelial filaments that represent the fungus's vegetative stage. Once the seed germinates, the filaments initiate their growing phase, rapidly extending through the stem and leaf cells of the shoot's green tissue. Following the mature stage of the plant, the endophyte concentrates mostly in the leaf sheaths, and advances towards the flower stem when the reproductive phase approaches.

Finally, the endophyte concentrates in the flower heads, where it invades the tissue of the ovaries and ovules, and remains to infiltrate the seed embryo and secure its path towards the next generation (Ball et al., 1993**).** As a result of the endophyte's metabolic activities, various secondary bioactive compounds classified as alkaloids are generated. These alkaloids play various roles within the plant, such as providing support with active feeding deterrents to herbivorous insects and nematodes that attack its root system. Ergot alkaloids also cause an amplified osmotic adjustment and nutrient accumulation that, in addition to an improved root and leaf physiognomy, improve water conservation to aid in developing tolerance to drought. The symbiotic relationship also allows tall fescue to withstand overgrazing conditions (Ball et al., 2003) and intensify its photosynthetic activity in response to the energy requirements of the fungus and its host (Rozpądek et al., 2015).

The alkaloids produced by the *Epichloë* species are divided into four classes: indole-diterpenes, peramines, lolines, and ergot alkaloids. Each of these chemical compounds have been found to have specific functions that are beneficial for the symbiotic relationship. Lolitrem B is identified as the indole-diterpene causal agent of ryegrass staggers in mammalian herbivores. Peramines are recognized as an effective insect deterrent (Bush et al., 1997), and Siegel et al. (1990) reported a potent insecticidal action from loline alkaloids in an aphid bioassay. Further, ergot alkaloids that infect tall fescue produce a variable level of toxicity to herbivores that graze on it (Young et al., 2014). All naturally-originated ergot alkaloids are characterized for having an ergoline ring system (Flieger et al., 1997), and depending on their tetracyclic structure can be further divided into clavines, ergoamides or ergopeptines. These structures facilitate the interaction with multiple receptors in the central nervous system and adrenergic receptors found in blood vessels, due to their resemblance to neurotransmitter molecules such as dopamine, serotonin and noradrenaline (Wallwey and Li, 2011). Both ergoamides and ergopeptines are derivatives of lysergic acid (Gerhards et al., 2014), but several studies have reported that ergopeptines are the main causative agent of fescue toxicosis in grazing livestock (Strickland et al. 2011). Within these ergopeptines, ergovaline has been identified as the predominant compound (Yates et al., 1985; Lyons et al., 1986). TePaske et al. (1993) found in analyzed endophyte-infected tall fescue samples, ergovaline represented the largest amounts in both forage and seed samples, while ergosine, ergotamine and ergocryptine were also found in smaller portions.

Furthermore, these alkaloids have a variable distribution throughout the plant and change depending on its developmental stage. In the reproductive stage of tall fescue, ergot alkaloid concentration correlates to the mycelial abundance. *E. coenophiala* mycelia are highly concentrated in the basal stem tissue and in the seed gametes, and found in lesser amounts in the sheath and ligular area. Ergovaline concentrations are found in higher abundance in the seedhead and decrease significantly in the sheath, leaf, and root tissue (Kenyon et al., 2018). In addition, research done by Kenyon et al. (2018) reported differences on the vegetative canopy and vertical distribution of ergot alkaloids in endophyte-infected tall fescue, where the highest concentration of ergovaline and total ergot alkaloids was found in the 0 to 5 cm canopy portion, with a significant alkaloid reduction above that height. Ergot alkaloid concentrations also have seasonal variation that follow the growth sequence of the plant. Ergovaline concentration has an ascending pattern that begins in the spring and reaches its highest peak in the fall period. Alternatively, total ergot alkaloid concentrations show a bimodal distribution, reaching an initial peak in late spring to further decrease as the plant enters a lethargy phase during the summer, and repeating an increase to maximum concentration in early fall (Rogers et al., 2011). Further, ergot alkaloid concentration in autumn-stockpiled fescue has been shown to decrease as winter progresses, which provides an opportunity for producers to utilize their pastures for grazing livestock during the winter, reducing negative effects of the alkaloids and increasing profitability by reducing feeding costs (Franzluebbers and Poore, 2021). Alkaloid concentrations may also fluctuate depending on changes in environmental temperature and precipitation. Exposure to warmer environmental temperatures for a prolonged period of time has shown to significantly increase ergot alkaloid concentrations by 30-40% in tall fescue. Interestingly, this increase in temperature may also be detrimental to the plant species dominance in an ecosystem, as warming seemed to induce a significant reduction in relative abundance of tall fescue within a specific pasture ecosystem (McCulley et al., 2014). Evidently, several variables must be assessed to determine appropriate management strategies for tall fescue pastures, in order to obtain optimal productivity from their utilization.

Management of Endophyte-Infected Tall Fescue and Alternatives

The Southeast region of the United States is commonly referred to as the “Fescue belt” due to its extensive presence in this area and its use in pastures for grazing, stockpiling and stored forage as haylage and hay. Considering the previously described positive and negative characteristics that tall fescue offers, different strategies have been developed to manage this forage and ameliorate the undesirable effects of toxicosis in livestock. Diversification of plant species present in pastures has been evaluated as a means to reduce the alkaloid effects in domestic herbivores and increase their productivity. Interseeding with legumes and other grasses increases the nutritional value and forage availability during the low production stages of fescue (Kallenbach, 2015). Grain and protein supplementation is another nutritional approach widely practiced. Aiken et al. (2008) reported a cost-effective increase in weight gains of steers that grazed endophyte-infected tall fescue and were supplemented with pelleted soybean hulls, but showed no evidence of reducing the effects of toxicosis. Elizalde et al. (1998) described an improvement in average daily weight gain of endophyte-infected tall fescue grazing steers that were supplemented with cracked corn grain and corn gluten feed. Considering the elevated concentrations of ergovaline in the seed heads and basal tillers of tall fescue reported by Kenyon et al. (2018), special consideration should be given to grazing management in order to avoid intake from livestock of this specific portions. Additionally, grazing on non-toxic pastures during the summer, combined to an effective paddock rotation and mowing of seed heads during the vegetative stage of fescue in the spring and the fall are all recommended pasture management practices (Roberts and Andrae, 2004). Fertilizer applications should be carefully planned as well. Nitrogen is commonly used as a growth promotant in pastures, but various studies have concluded that excessive applications of nitrogen can exacerbate the production of ergot alkaloids in tall fescue (Kallenbach, 2015). Lyons et al. (1986) found that the application of high-concentrated nitrogen fertilizers to tall fescue plants correlates to higher rates of ergot and ergopeptine alkaloids, and Rottinghaus et al. (1991) reported that ergovaline quantities increased in leaf sheaths, leaf blades and seed heads following nitrogen fertilization. Furthermore, a common practice in Southeast farms is processing tall fescue into hay and haylage as a means to increase feed availability during winter months. Forage moisture falls below 20% during hay-making to increase its quality and durability. This process also impacts ergot alkaloids, which are degraded by oxidation and exposure to sunlight. Compared to fresh chop and ensiled tall fescue, hay can have substantially less ergot alkaloids. Nonetheless, in most cases the remaining load of toxic alkaloids in tall fescue hay will still be detrimental to livestock that consume it (Kallenbach, 2015). An additional process that has proven to increase nutritional quality and reduce alkaloid concentration in tall fescue hay is ammoniation, which involves adding anhydrous ammonia to covered hay bales over a period of 3 to 6 weeks (Roberts and Andrae, 2004).

Another alternative developed by plant breeders are endophyte-free and novel endophyte varieties of tall fescue. Endophyte-free cultivars do not produce the toxicosis symptoms in livestock due to the absence of fungal symbiosis. Animals that graze on it have a better performance and productivity. However, removing the endophyte has a negative impact on the plant because it makes it more susceptible to pests and adverse environmental conditions reducing stand longevity. As a solution, alternate tall fescue varieties have been developed by replacing the toxic endophyte with new, beneficial endophyte strain that produce less or no ergot alkaloids yet still support the stress tolerance of the plant. Livestock that graze on pastures with these non-toxic fescue varieties report improved gains and reproductive performances compared to animals that consume alkaloid-infected fescue. Replacing infected fescue pastures with either one of the non-toxic alternatives is a major cost for producers, considering the workload and resources needed, in addition to the prolonged period in which the pasture will not be available for grazing. Moreover, these fields also require a different management strategy in order to prolong the cultivar's persistence and avoid a reinfestation of fescue species that produce ergot alkaloids (Ball et al., 2003; Roberts and Andrae, 2004; Kallenbach, 2015).

Effects of Fescue Toxicosis on Cattle Performance

Fescue toxicosis is syndrome caused by the intake of endophyte-infected tall fescue by cattle. In the United States, it is estimated that economic impacts associated to this health issue account for approximately $2 billion every year (Kallenbach, 2015). The alkaloid metabolites, predominantly ergovaline, produced by the symbiotic relationship trigger several unfavorable effects on physiological mechanisms within grazing cattle. These problems vary in mode of action and severity as the mycotoxins interact with the organism and are degraded through digestive, absorption and metabolic processes. As previously stated, oral ingestion is the principal route of intoxication for cattle, and the amphipathic properties of ergot alkaloids greatly determine the rate and extent of their absorption (Strickland et al., 2011). Following molar trituration, the ergot alkaloids present in forage are swallowed and moved into the ruminal cavity, where microbial fermentation and digestion processes increase the solubility and availability of the total ergot alkaloids, transforming them into simpler ergopeptine alkaloids, such as ergovaline and lysergic acid (Ayers et al., 2009). De Lorme et al. (2007) also reported that ruminal microbial action in sheep can further degrade ergovaline into lysergic acid. In addition, Hill et al. (2001) suggest that apart from the rumen, ergot alkaloids are also metabolized in the reticulum and omasum chambers. Lysergic acid and ergoline are absorbed at a faster pace in the rumen compared to the other ergopeptine alkaloids, which are transported in the digesta to the forestomach and the intestinal system to complete the nutrient assimilation process. Evidence suggests that in ruminants and non-ruminants, the small intestine is the primary organ for ergopeptine alkaloids absorption (Strickland et al., 2011). Following ruminal and enteric absorption, the ergot alkaloids are released into the blood stream and transported to the liver, where metabolization continues and a process of sorting occurs, in which the large ergopeptine alkaloids are carried to the bile for further processing and excretion in fecal matter, while smaller compounds like ergoline and lysergic acid flow to the kidneys to be excreted in the urine (De Lorme et al., 2007). In the past, it was assumed that ergovaline was the exclusive ergot alkaloid responsible for inducing the symptoms of fescue toxicosis (Yates et al., 1985). More recently, this theory is being reconsidered due to the identified diversity in types of ergot alkaloids and the previously described metabolic processes that these compounds undergo in the ruminant digestive tract (Hill et al., 2001; De Lorme et al., 2007; Ayers et al. 2009; Strickland et al., 2011).

As the ergot alkaloids are metabolized and transported to different tissues and organs, several negative effects arise affecting cattle performance. Physiologically, an interaction has been identified between ergot alkaloids and different biogenic amine receptors, and these alkaloids can have variable agonist, partial agonist, and antagonist effects (Berde and Stürmer, 1978). These associations are facilitated by the similarities in chemical structure that ergot alkaloids share with endogenous neurotransmitters, such as adrenergic, dopaminergic and serotonergic receptors in different species and environmental conditions (Klotz, 2015). Among the tall fescue alkaloids, ergovaline, ergotamine and ergocryptine have shown similar binding characteristics to D2-dopamine receptors in cell culture, which reduce the availability of receptors and directly inhibit the secretion of cyclic AMP, prolactin, serotonin, and indirectly affect insulin secretion (Larson et al., 1999; Strickland et al., 2011). In consequence, one of the symptoms that cattle affected by fescue toxicosis show is reduced concentrations of serum prolactin (Parish et al., 2013). Furthermore, the reduction in prolactin concentrations is a relevant concern in beef cattle operations because this hormone plays an important role in regulating lactation, body hair coat growth and shedding, and body temperature (Littlejohn et al., 2014). A correlation exists between ergot alkaloid consumption and decreased prolactin production, which is caused by the antagonist effect of ergovaline in the dopamine pathway, disabling proper hormone binding to its receptor. In consequence, this disruption provokes some of the symptoms associated with fescue toxicosis, such as decreased milk production, retention of winter hair coat, and increased body temperatures (Porter and Thompson, 1992).

Amidst the ergopeptines identified in tall fescue, ergovaline is the most abundant and potent alkaloid, making it the central focus of research done on fescue toxicosis (Guerre, 2015). This ergot alkaloid is a vasoactive compound that has vasoconstrictive effects that alter the normal functioning of the circulatory system (Alfaro and Moisá, 2022). Sensitivity to ergovaline varies among ruminant species, with sheep being more tolerant than cattle, and it will also be influenced by health and environmental conditions. A threshold for cattle has been established indicating 400-750 ppb (1 ppb = 1 ng/kg) of ergovaline will induce clinical symptoms (Tor-Agbidye et al., 2001). However, under heat stress conditions this tolerance range can decrease to 200-350 ppb (Hovermale and Craig, 2001). In addition to ergovaline, there are other alkaloids related to vasoconstriction. Pesqueira et al. (2014) found that ergopeptine alkaloids can induce and sustain contractile responses, with ergovaline and ergotamine causing the most potent and durable contractions in a bovine saphenous vein bioassay, and suggesting a possible accumulation of the toxin that might prolong the toxicosis effects hence delaying the recovery. Klotz et al. (2007) reported a potential bioaccumulation of ergovaline and ergotamine related to slow alkaloid dissociation from serotonin receptors, which may be the principal cause of vasoconstriction related to fescue toxicosis. Effects produced by alkaloid-induced vasoconstriction are well documented. Aiken et al. (2009) confirmed this theory via doppler ultrasonography, as their results showed a lower heart rate and reduced blood flow in caudal arteries of beef heifers that were previously exposed to diets containing ergot alkaloids. One of the major consequences is the reduced blood circulation to peripheral vasculature, which causes lameness and gangrene in the extremities, and fat necrosis (Waller, 2009) that considerably perturb normal mobility and performance in cattle. The gangrenous ergotism, one of the most visually evident consequences of fescue toxicosis, induces necrosis in ear, tail and hoof tissue, and in severe cases can lead to loss of the affected extremity or the entire animal (Klotz, 2015).

In addition, vasoconstriction has a negative impact on normal ovarian function and pregnancy establishment, which in consequence also reduces productivity in cow-calf operations. Some of these offsets may be a limited nutrient transport and intake, abnormal functioning of the hypothalamus, hypophysis, and pineal glands, and concomitant alterations on the ovaries and the estrous cycle (Strickland et al., 2011). Lyons et al. (2018) observed a significant reduction in the diameter of arteries and veins that transport blood to the ovary and uterus of beef heifers after consuming a ration containing endophyte-infected fescue seed. Progesterone concentrations are also reduced in female cattle grazing endophyte-infected fescue pastures, consequently complicating the establishment of pregnancy and increasing the risk of abortion. Mahmood et al. (1994) described a significant reduction on serum progesterone levels on crossbred beef heifers grazing in a high endophyte-infected fescue pasture trial. Furthermore, an age difference in sensitivity to alkaloid exposure, as weaned heifers had lower progesterone concentrations compared to yearling heifers. This decrease in progesterone levels may be linked to local vasoconstriction of blood vessels that limits normal circulation of the hormone in the blood stream. Moreover, ergot alkaloid effects on the male reproductive tract are yet to be elucidated. Pratt et al. (2014) reported that bulls grazing on endophyte-infected fescue pastures had reduced weight gain, lower serum prolactin concentrations, inferior sperm concentration and increased morphological abnormalities in ejaculate samples, reducing the overall semen quality and freezing potential. However, additional research is necessary to fully comprehend the effects of fescue toxicosis on bull reproductive performance, especially in the Southeastern U.S. where

95% of cow-calf operations use natural service during the breeding season (Pratt and Andrae, 2015).

Ergot alkaloids also negatively impact the ruminal and intestinal microbiome. As it was previously described, the level of alkaloids present will vary depending on the maturity stage of tall fescue plants. The ergot alkaloids contained within the forage are exposed as it follows the rumination process and initiate an interaction with the different species of microorganisms distributed along the digestive tract. Previous research by Moyer et al. (1993) and Harlow et al. (2017) found alkaloid susceptibility to ruminal degradation in their respective in vitro and ex vivo studies. Despite this degradation, there is evidence that ergot alkaloids, principally ergovaline, can still induce vasoconstriction in the ruminal vessels (Foote et al., 2011) and also limit blood flow to the duodenum, colon, and kidney of cattle (Rhodes et al., 1991). From a nutritional perspective, sufficient blood flow to the ruminal and gut surfaces is necessary for an adequate absorption of nutrients. During fescue toxicosis, this mechanism is disrupted and compromises volatile fatty acid (VFA) absorption and metabolism, consequently leading to decreased weight gain and growth performance in ruminants. In addition, an augmented microbial interconversion of the VFA may negatively impact feed efficiency, as methanogenesis could be potentially increased in the rumen as a consequence of the decreased absorption of VFA (Foote et al., 2013). Further, Mote et al. (2022) stated that endophyte-infected tall fescue modified the ruminal microbiota in grazing steers, by reducing the quantity of fungi species that directly engage in cellulose degradation and digestion, which ultimately may affect ruminal passage rates. Ergovaline has also been associated as a disruptor of microbiota diversity in the gut of cattle that grazed on alkaloid infected fescue pastures by reducing the number of microbial species. More notably, this susceptibility to the alkaloid was incremented under heat stress conditions, indicating an interaction between the toxin and environmental conditions that influence the animal response to the toxicosis syndrome (Mote et al., 2020).

The repercussions that ergot alkaloids have on the immune system are multiple, and consequently trigger several negative impacts on cattle operations. Cattle that graze on endophyte-infected pastures show reduced body weight and average weight gains (Parish et al., 2013; Wilbanks et al., 2021), which lead to a decreased intake of nutrients that are necessary for adequate functioning of the immune system. Following exposure to a pathogenic infection or tissue injury, the immune response is activated by the surge of inflammatory mediators, which include various cytokines, chemokines and prostaglandins. These compounds regulate the inflammatory response by stimulating and orienting the activity of immune cells and mediators that eliminate infectious agents and damaged cells, and proceed to restore affected tissue (Sheldon et al., 2014). Most of these mediators, especially cytokines, are soluble factors that may be either released by most cells into the circulatory system or directly into tissue or remain within the cell to act as integral membrane proteins (Dinarello, 2007). Proinflammatory cytokines are known to be associated with reduced levels of prolactin in blood serum, increased body temperature as they are pyrogenic compounds, and may be related to the vasoconstrictive effects of fescue toxicosis due to their inflammatory nature (Filipov et al., 1999). Poole et al. (2019) reported a hyperactive innate immune response in stocker steers exposed to endophyte-infected tall fescue seed, which exhibited increased concentrations of pro- and anti-inflammatory cytokines when compared to the response of steers that were not exposed to the alkaloids. This translates to repercussions on major stressful events, such as weaning and immunization trials, as they become more challenging to overcome for calves that have been exposed to the toxins present in endophyte-infected tall fescue (Poole et al., 2019), thus forcing a suppressed antibody response to vaccinations (Dawe et al., 1997). Moreover, the antagonist effects of ergot alkaloids on prolactin pathways induce several scattered disruptions. In the immune system, it is known that white blood cells have prolactin receptors on their membrane, and lymphocytes are capable of secreting prolactin (Reber, 1993) and also possess dopamine receptors in their structure, which may have regulatory functions on prolactin production and release that are key for appropriate immune responses (Freeman et al., 2000). In addition, prolactin is also involved in lactogenesis and mammary gland differentiation mechanisms in cattle. As it was previously stated, reduced serum prolactin levels and decreased milk production are common symptoms associated with fescue toxicosis. However, prolactin is not directly responsible for maintaining milk production in lactating cows (Porter and Thompson, 1992). Consequently, the decrease in milk production associated with fescue toxicosis is not directly related to the prolactin concentration reduction, but may be associated with other detrimental symptoms of the syndrome such as vasoconstriction and reduced feed intake (Poole and Poole, 2019). Further, Wilbanks et al. (2021) reported that pregnant cows grazing on endophyte-infected tall fescue pastures had reduced weight gain during the last gestational trimester, and a lower milk production during the first postpartum month that resulted in depressed calf weight gains. Depressed prolactin concentrations are also related to the retention of winter hair coats in cattle during the summer. When unaffected, prolactin is a hormone directly associated with photoperiod, meaning that its concentrations increase with increasing daylight hours (Karg and Schams, 1974). Porter and Thompson (1992) also associate prolactin with winter hair growth in the fall and early winter, as daylight time shortened, and with hair coat shedding in the spring and early summer, as daylight hours extended. More recently, a mutation in prolactin signaling has been found to be a direct modulator of the length and weight of hair, and also the sweat rate in cattle. Further, cattle carrying these mutant transcripts show an association between prolactin and thermoregulation processes, suggesting that the protein hormone might control sweat secretion in addition to coat length (Littlejohn et al., 2014). McClanahan et al. (2008) found that yearling calves grazing on endophyte-infected tall fescue experienced lack of shedding and continued hair growth during the summer months, which could be linked to depressed prolactin concentrations. These calves also had lower weight gains, reduced sweating rates and shorter grazing intervals during periods of high environmental temperature and humidity. Aiken et al. (2011) reported an increased effect of hyperthermia attributed to rough hair coats in steers that grazed toxic fescue during the summer. However, they attribute the coat thickness to be caused by hair retention from the winter and excessive hair growth during longer summer days. Despite the cause, heat stress induced by retained hair coats increases the vulnerability of cattle that graze endophyte-infected pastures during the summer.

Ruminants excrete ergot alkaloids through urine and fecal matter. Different hepatic, biliary and renal metabolic processes take place to remove ergot alkaloids from blood circulation and lead to detoxification (Klotz, 2015). According to Eckert et al. (1978), the elimination pathway for ergot alkaloids is dependent on the molecular weight of each compound. Ergot alkaloids under 350 Da are removed via the renal system, whereas compounds weighing over 450 Da, such as ergovaline and other ergopeptine alkaloids, are eliminated via the biliary system and excreted with the feces. Furthermore, previous evidence indicates that ergot alkaloids elimination via milk occurs in isolated cases of extremely high intake of these toxic compounds, and most likely is not a principal route for excretion. Previous studies also indicate that despite the metabolic and physiological efforts of the animal to remove the consumed toxic alkaloids, only a partial elimination is possible (Klotz, 2015). When comparing the ingestion and excretion of ergovaline and lysergic acid in crossbred steers consuming high-alkaloid tall fescue straw, Merrill et al. (2007) reported a higher intake of ergovaline, but a higher excretion of lysergic acid. This partial recovery of the consumed ergovaline from the excreta suggests a possible degradation process converting it to lysergic acid, which might correlate to having a greater excreted amount of lysergic acid than was consumed.

Different researchers have evaluated if detoxification from fescue toxicosis in livestock is possible and what the duration of these timeframes would be. Cattle may recover from most symptoms, excluding gangrene and necrosis of tissue, by removing the source of the ergot alkaloids. Recovery times for body temperatures in cattle will likely be influenced by the environmental temperature and humidity index, and might fluctuate between one and four weeks, whereas prolactin concentrations might increase to normality in a two-week period (Aiken et al. 2013). Vasoconstriction effects on the caudal artery have variated among studies. Klotz et al. (2016) reported changes in peripheral vasoactivity and recovery from vasoconstriction in steers 36 days after being removed from endophyte-infected pastures. In contrast, Aiken and coworkers (2013) indicated that vasoconstriction of the caudal artery caused by ergot alkaloids was not relieved after relocating steers to a non-toxic diet for 30 days (Aiken et al., 2013). These differences might correlate to the possibility of alkaloids binding to specific receptors in tissue that impede their removal and could even give rise to bioaccumulation. More specifically, several studies evaluating contractile responses of bovine lateral saphenous vein evidence that the ergoline ring structure found in all ergot alkaloids facilitates the interaction with the different biogenic amine receptors. Further, these results indicate that contractile responses produced by ergopeptine alkaloids are more persistent, implying that compounds like ergovaline might be more difficult to metabolize and extend the recovery period (Klotz, 2015). However, more research is needed to confirm if bioaccumulation of ergot alkaloids in different tissue and body fluids persists for extended periods.

Animal Management Strategies to Mitigate Fescue Toxicosis

Animal health, performance and profitability are all parameters affected by fescue toxicosis. To reduce the negative effects caused by this disease, efforts have been made to increase the understanding of the multiple interactions between endophyte-infected tall fescue and cattle that consume it, with the ultimate objective of identifying strategies that can increase animal productivity and welfare. Historically, researchers and producers have focused their interest and work on a bilateral approach to counteract the negative effects produced by the ergot alkaloids contained in tall fescue, the first aiming to develop pasture-based solutions and the second targeting animal-based solutions. As pasture-based strategies were addressed earlier in this review, the following segments will center on describing the different animal-based strategies available. These methods are based on multiple approaches focusing on nutritional supplementation, specific management practices, genetic and breeding management and genomic identification of traits associated to the disease. Producers have used energy or protein feed supplementation during grazing with the objectives of increasing animal performance, improving and extending the availability of forage in pastures, increasing stocking rates, and in an endophyte-infected pasture scenario, to dilute the load of alkaloid intake from tall fescue. Carter and coworkers (2010) evaluated the effects of supplementing pelleted soybean hull, which is a byproduct protein feed ingredient, on steers grazing endophyte-infected tall fescue pastures. It has been reported that at the end of the two-year study, the group of steers consuming soybean hull pellets had greater average daily weight gains, increased serum prolactin concentrations, and tended to have sleek hair coats (Carter et al., 2010). Correspondingly, Aiken et al. (2008) also reported that supplementation of soybean hulls to steers grazing endophyte-infected tall fescue pastures increased their average daily weight gain, but did not observe differences in hair coat roughness and serum prolactin concentrations. It is also valid to state that the incorporation of nutritional supplements will increase production costs. A complementary approach is to establish specific herd management strategies based on identifying the adequate periods in the calendar where maximum benefit can be obtained from the available resources in the operation. One strategy that has proven substantial improvements is deferring the calving season from the spring to the fall. In the past, beef producers developed their breeding plans with the objective of having calves born during the spring, coinciding with the increase in forage resources and their capacity to satisfy the increasing nutritional demand of lactating cows. However, this specific timeframe also concurs with the growing and reproductive phases of tall fescue, which are the periods when the ergot alkaloid concentrations reach the highest peaks in the plant. Consequently, exposing cattle to these ergot alkaloids during the spring increases their susceptibility to heat stress, vasoconstriction, and other previously stated maladies during the higher temperatures of the summer, negatively impacting the herd productivity. By postponing calving season to the fall, cow-calf grazing operations avoid this exposure to high levels of ergot alkaloids during critical periods and are able to maintain productivity. Further, this strategic adjustment to fall calving has reported to reduce calving intervals by 11 days, on average, when compared to spring calving (Caldwell et al., 2013). Caldwell and coworkers (2013) attribute these differences to seasonal decrease in environmental temperatures, in addition to a change in toxin concentration of tall fescue during a period when cow nutritional requirements are extreme. These positive results also correlated to calf performance in this study, with fall-born calves having higher average daily weight gains, weaning weights, and overall increased productivity than calves born in the spring (Caldwell et al., 2013). Based on this evidence, producers who utilize tall fescue as the main forage source may profit from implementing fall calving to increase animal performance and productivity in their operations.

Different investigations have focused on identifying animals that have reduced susceptibility to ergot alkaloid toxicosis from tall fescue intake. One of the approaches utilized has been evaluating the performance of *Bos indicus* breed of cattle under the effects of fescue toxicosis, due to their recognized increased resistance to heat stress and ability to thrive in adverse environments. Superior performance has been reported from Brahman-cross cattle compared to British cattle breeds when grazing endophyte-infected tall fescue pastures. Goetsch et al. (1988) stated that Brahman crossbred steers had increased average daily weight gains compared to English crossbred steers (Goetsch et al., 1988). Similarly, Brown et al. (2000) reported that Brahman-cross cows consuming endophyte-infected tall fescue demonstrated better tolerance to the toxin deleterious effects than purebred cows (Brown et al., 2000).

Moreover, positive differences indicating tolerance have also been found in specific *Bos taurus* breeds. The Romosinuano, which are a tropically adapted breed developed in Colombia from Spanish cattle, have been described to possess increased resistance to heat stress. Cows of this particular breed were utilized in a trial to compare their tolerance to endophyte-infected tall fescue consumption relative to Angus cows. The results indicated that despite having decreased milk production and serum prolactin concentrations attributed to ergot alkaloids, Romosinuano cows had lower rectal temperatures than Angus cows (Burke et al., 2010). Another breed that has been shown to reduce the negative consequences of fescue toxicosis is the Senepol. This composite genetic line was developed from crossing Red Poll and N’Dama animals, and are renowned for their increased capacity to tolerate high environmental temperatures. This heat resistance ability is facilitated by the presence of a slick gene, which is affected by the prolactin receptor mutation, and is expressed phenotypically as a permanently short, slick hair coat that permits a more efficient thermoregulation capacity. This slick trait might have positive implications in offsetting some the negative symptoms, such as retained winter hair coat and increased body temperature, associated with fescue toxicosis and improving reproductive performance. Poole et al. (2017) studied the impact of the slick hair trait in physiological and reproductive parameters in crossbred Angus-Senepol heifers consuming endophyte-infected tall fescue haylage. Their results indicated that the group of heifers that had a normal hair coat gene and consumed ergot alkaloids in their respective diets had a decreased number of dominant follicles, compared to groups of slick gene heifers consuming alkaloid-free diets (Poole et al., 2017).

Cattle responses to diseases like fescue toxicosis have also been reported to differ between different regions. Studies that utilized different beef and dairy cattle breeds identified that the region of origin had an effect on the animal response to heat stress (Carvalho et al., 1995, Huang et al., 2008). Furthermore, Johnson et al. (2014) declared regional differences in stocker cattle responses to consumption of endophyte-infected tall fescue seed. Angus steers from Missouri, a state that is part of the Fescue Belt, had a minor reduction in feed intake when fed toxic tall fescue compared with nontoxic tall fescue, when compared to Angus steers from Oklahoma, which were considered naïve to fescue toxicosis due to the absence of tall fescue in this state (Johnson et al., 2014). This evidence supports the criteria that cattle populations might be capable of developing certain level of tolerance to diseases like fescue toxicosis following exposure to the causal agent for extended timeframes. However, a well-defined genetic approach to identify and select these specific groups of animals is yet to be identified and developed to disseminate to beef cattle operations.

Genetic Advancement for Fescue Toxicosis Resistance

Over the last decade, significant progress has been done in genetic and genomic tools that have been used to increase productivity in beef cattle operations. These techniques have also been used to understand the genetic properties and mechanisms associated with fescue toxicosis. Two different perspectives have received interest among research objectives: phenotypic selection and genomic selection. Both approaches share a common objective of identifying groups of animals within a population that have demonstrated traits of tolerance or resistance to the symptoms related to fescue toxicosis and to phenotypically and genotypically evaluate these specific individuals in order to detect the responsible traits conferring this superiority (Smith and Cassady, 2015). Nonetheless, the complexity of the symptoms expressed by cattle following exposure to ergot alkaloids in tall fescue, and their interaction with diverse environmental factors, generates a wide variability within herds and ravels the possibility of developing an accurate and consistent method to identify these fescue tolerant animals make genetic progress in offspring. One of the phenotypic strategies that has gained acceptance in recent years has been selecting cattle based on their hair shedding capacity. As it was previously discussed in this review, winter hair coat retention associated to low serum prolactin concentrations is one of the most evident symptoms of fescue toxicosis, which increases the animal susceptibility to heat stress (Porter and Thompson, 1992; McClanahan et al., 2008). This peculiarity motivated Gray et al. (2011) to investigate the variation in hair coat shedding of Angus cows following exposure to endophyte-infected tall fescue and develop a method to rate this shedding ability. Their research project utilized 532 Angus cows dispersed in two locations and implemented the use of a numeric scale from 1 to 5 to score the hair shedding, with 1 representing a fully-slick, summer hair coat and 5 representing a rough, winter hair coat. The score evaluation was performed every 30 days from March to July for three consecutive years. Following data collection and analysis, a threshold was established for cows averaging a score of 3 or lower by the beginning of June, defining them as “early shedders”, while cows with higher scores were defined as “late shedders”. Additionally, researchers also identified an average increase of 11.1 kg, in adjusted weaning weight of calves born from early shedding dams. In terms of heritability, it was found that hair shedding ability is moderately heritable (h^2=0.35), while a strong correlation between adjusted weaning weight and dam shedding ability was identified to have a high repeatability at 0.65 (Gray et al., 2011). This study also concluded that hair shedding variation within the cow population was still evident subsequent to grazing of endophyte-infected pastures. Furthermore, calf weaning weight results obtained by Gray et al. (2011) were reported to the American Angus Association, so they could perform calculations and provide adjusted 205d weaning weights, which take into account the age of dam and age of calf to 205 days. Based on the evidence published by this study, the American Angus Association released in May of 2022 a new production EPD for Hair Shedding (HS). The HS EPD is expressed in units of hair shed score, with lower EPD values indicating a more favorable capacity of the animal to shed their winter hair coat earlier in the spring (Angus Newsroom, 2022). This EPD, in addition to a well-established shedding score scale, provide relevant and efficient tools of selection that enables producers to improve identification of more efficient and productive animals within their herds, leading to a better selection of replacement females, and appropriately select sires that will produce the next generation of cattle in their operation.

The technological upgrades in genomic selection tools have provided a different perspective to analyze specific genes and genetic markers that are linked to fescue toxicosis tolerance in cattle. Most of the studies done in this area have focused on investigating single nucleotide polymorphisms (SNPs), which are recognized as variations within the base pairs of a DNA sequence. Prior to assessing SNPs, candidate genes have to be identified based on general association to a disease of interest (Patnala et al., 2013). In the specific case of fescue toxicosis, one of the candidate genes that has been investigated for correlation with tolerance or susceptibility is the prolactin gene. Looper et al. (2010) collected genomic DNA samples from purebred Angus, Brahman, and their reciprocal cross cows and calves that grazed either bermudagrass or endophyte-infected tall fescue pastures throughout their lifetime. Polymorphisms were specifically analyzed in the enhancer region of the bovine prolactin gene, where two SNPs were identified. One base pair had a cytosine to thymine variation (c1286t) defined as a major allele, while the other base pair had an adenine to guanine variation (a1167g) defined as a minor allele. In the discovery population, it was found that cows that were consuming endophyte-infected tall fescue and had the homozygous thymine (TT) genotype at the major allele had reduced calving rates during their lifetime, in comparison to the other genotypes included in the analysis. This study also postulated the possibility of utilizing the relationship between the TT genotype and calving rate as a means to adopt selection for this genotype and increase profitability (Looper et al., 2010). Campbell and coworkers (2014) reported in a multi-study publication that an intronic polymorphism was discovered on the dopamine receptor D2 (DRD2) gene located in the bovine chromosome 15. This gene is strongly associated with prolactin secretion in bovine species, which consequently creates a link of interest to fescue toxicosis management. The authors collected data from four different experiments and used multiple herds from different establishments in Missouri and Tennessee. In one of the trials, 42 Angus-based steers were assigned to graze either endophyte-infected or novel-endophyte, non-toxic fescue pastures, and further genotype analyses were performed in the DRD2 gene. Results indicated that the SNP of steers homozygous for guanine (wild type) that were grazing on endophyte-infected pastures was related to decreased serum prolactin concentrations and elevated hair shedding scores. Additionally, results of a second trial utilizing spring and fall-calving Angus cows also found genomic differences at the DRD2 gene, in which cows that belonged to the spring-calving group increased fescue toxicosis symptoms after grazing endophyte-infected pastures. Based on this evidence, the authors suggest that the DRD2 SNP may provide advantages in cattle selection for resistance to fescue toxicosis (Campbell et al., 2014).

More recently, a more commercial alternative test was released by AgBotanica, LLC (Columbia, MO), which utilizes a SNP genomic approach to detect genetic variation in animals exposed to ergot alkaloids that can lead to the identification of tolerant individuals to fescue toxicosis. This genetic test, called T-Snip, was evaluated by Masiero et al. (2016) in a study as a means to predict 205d weaning weights of calves born from dams consuming endophyte-infected tall fescue. Their results indicated a significant positive correlation between the T-Snip scores to calf weaning weights, suggesting the T-Snip analysis as a potential indicator of tolerance to fescue toxicosis (Masiero et al., 2016). Nonetheless, one of the major limitations of the T-Snip genetic test is its proprietary restrictions, which implies that information about animal performance and infection rates, breeds, and seasonal measurements have restricted access. A subsequent study by Galliou et al. (2016) evaluated the effectiveness of the T-Snip test to identify animals with genetic variation for fescue toxicosis tolerance. They utilized 148 pregnant

Angus cows at two different locations were exposed to endophyte-infected tall fescue pastures and evaluated for weekly body weight gain for 13 consecutive weeks. In contrast to the results published by Masiero et al. (2016), this study indicated the T-snip test may be an efficient method to predict cow performance, but, does not accurately identify animals with genetic potential for tolerance to fescue toxicosis (Galliou et al., 2016). Accordingly, a study by Alfaro et al. (2021) in beef dams also concluded that the T-snip test does not provide effective results to differentiate between tolerance and susceptibility to this disease (Alfaro et al., 2021). Based on this evidence, additional research is necessary to identify other candidate genes and polymorphisms that are associated to the genomic aspects of fescue toxicosis. As new technologies are developed, further research opportunities will arise to strengthen genomic identification using SNPs on animals that can provide more efficient alternatives to reduce the consequences of fescue toxicosis and improve productivity of beef cattle farms in the Fescue Belt.

Potential Use of EPDs to Identify Fescue Toxicosis Resistance in Beef Cattle

Advancements made in the field of genomics have enabled researchers and producers to implement strategies for genetic improvement more efficiently in cattle operations. Genetic management strategies utilize computer-based estimates of the animal genetic value and compares it to different values of traits associated to productivity. These genetic estimates are generated by taking into account both individual performance records, the pedigree information of all relative progeny data, as well as genomic information. Most of these individual and collective data are recorded by members of a specific breed association, and then are submitted for genetic evaluation. Based on these analyses, breed associations report specific EPDs, which are adjusted for the effects of age, sex, and other non-genetic effects. These genomic-enhanced

EPDs (GE-EPD) increase their accuracy and provide producers the opportunity to genetically improve their herds in a more efficient manner (Gonda, 2020). Accuracies of GE-EPDs are also relevant because they account for the selection risk that producers assume when selecting the animals that will be bred and produce the next generation, as their scores are based on the amount of performance records associated to each individual. This implies a direct correlation between the number of records analyzed and the accuracy value for each EPD in the animal profile, with accuracy scores closer to 1 indicating more reliable prediction of genetic merit and scores closer to 0 indicating lower accuracy. EPD analyses also take into account the heritability of each trait by interpreting the additive genetic variation affecting differences in performance. Thus, a highly heritable trait will require less individual performance records to calculate its selection accuracy, while a lowly heritable trait will need more performance records to support its accuracy (Gonda, 2020).

Presently, most breed associations in the United States publish EPD information in their catalogues to provide this information to producers. Usually, these traits will be classified in categories targeting production, management, carcass, maternal, and efficiency parameters. Within each of these categories, different associated predictor EPDs can be utilized to develop genetic improvement strategies by producers to increase their herd productivity. From a scientific perspective, EPDs have also been included and/or generated in different research to evaluate their relevance on the objectives and interests of the investigations. For instance, researchers in the Southeast have investigated the impact of EPDs on fescue toxicosis management. Gray et al. (2011) identified a hair coat shedding variation within a herd that allowed to develop a hair coat shedding scale that can be utilized as a selection tool for fescue tolerance (Gray et al., 2011). Based on the moderate heritability of the hair shedding trait, the

American Angus Association published a HS EPD that allows producers to identify animals within their herd and candidate sires that have lower HS EPD scores. This indicates an increased capacity to shed their winter coats earlier in the spring, thus providing an advantage to better cope with high temperatures during the summer and increase the environmental adaptability to endophyte-infected fescue grazing (Angus Newsroom, 2022). In a different study, Poole et al. (2020) accurately identified tolerant animals to fescue toxicosis within a herd by utilizing phenotypic performance parameters. The experiment consisted in exposing purebred, pregnant Angus cows to endophyte-infected tall fescue pastures for 13 consecutive weeks. The evaluated phenotypic performance parameters included body weight, body condition score, hair coat score and hair shedding score. Based on the results obtained, the team of researchers decided to perform a subsequent analysis to designate cows into tolerant or susceptible groups. Results showed significant differences, with cows deemed tolerant showing greater average daily weight gains, and lower hair coat and hair shedding scores when compared to susceptible deemed cows (Poole et al., 2020).

An EPD has also proven effective for selection of resistant animals to high-altitude disease. High-altitude disease, commonly referred to as brisket disease, is a frequent condition experienced by cattle in regions with increased altitudes above sea level. It was previously thought that it only affected animals in elevations over 1,600 m, but different cases have been reported recently in more moderate elevations between 1,200 and 1,600 m (Pauling et al., 2018). High-altitude disease is exhibited as oxygen concentrations in the atmosphere decline with increased elevation, which causes an increase in effort by the cardiovascular system to compensate for the demand of oxygen supply. This additional stress has negative repercussions in the cardiopulmonary system, as bovine species are known to be inefficient in oxygen utilization. Consequently, the increased stress caused by alveolar hypoxia provokes pulmonary arterial vasoconstriction, which long-term exposure can develop changes in vascular walls, and in more severe cases induce right-side cardiac failure and death of the animal (Veit and Farrell, 1978; Holt and Callan, 2007). High-altitude disease has been documented since the beginning of the 20th century. The increased number of cases reported by producers motivated the Colorado Cattlemen's Association to initiate investigations in this matter, and in 1913 contacted George Glover and Isaac Newsom to lead the study. After two years of research, Glover and Newsom concluded that altitude was the main causative agent of high-altitude disease. Cattle grown in low altitudes which were relocated to higher-altitudes were more susceptible and developed worse symptoms from the disease. Moving affected animals to lower altitudes could reduce the negative effects, and cattle grown in low-altitude environments should be gradually introduced to higher elevations to allow for acclimation. The use of highland-born sires for breeding could provide a potential degree of tolerance of the disease to the herd, and high-altitude disease is related to cardiac exhaustion (Rhodes, 2005). Several decades later, following different work as a veterinarian, Rue Jensen discovered that cardiac failure in high-altitude disease was specific to dilation and malfunctioning of the right ventricle of the heart. Later on in 1956, Jensen and Robert Pierson did a collaborative research that concluded that pulmonary changes seen in high-altitude disease are caused by atmospheric hypoxia, which leads to augmented resistance to blood circulation through the pulmonary vessels and concludes with failure of the right ventricle. Jensen was also involved in a study with Archibald Alexander which confirmed the association of right ventricle hypertrophy to the increased weight in hearts of cattle suffering from high-altitude disease (Rhodes, 2005). Jensen and Alexander continued collaborating in studies focusing on the disease, and in an unforeseen alliance with other cardiologists Robert Grover and

John Reeves, and the physiologist Donald Will, discovered a linear relationship between the hypertrophy severity of the right ventricle and the intensity of mean pulmonary arterial pressure (PAP). As a result, they established a direct relationship between hypoxia, increased resistance in pulmonary vessels and right ventricle hypertrophy (Rhodes, 2005). Grover et al. (1963) evaluated the development of chronic pulmonary hypertension in cattle exposed to an elevation of 3,800 m. In this experiment, a group of cattle was administered 100% of oxygen to simulate acute hyperoxia. The results reflected that hypoxia-induced vasoconstriction contributed to the evolution of pulmonary hypertension, and that in the long-term hypoxia will increase the constriction capacity of pulmonary vessels. Additionally, it also concluded that removing the causal agent of vasoconstriction did not regress the mean PAP to normal levels, but instead could progress with time (Grover et al., 1963).

More recently, Holt and Callan (2007) reported a PAP test to identify tolerant animals to high-altitude disease. This procedure involves introducing a flexible catheter tubing through a large bore needle into the jugular vein and passing it down through the right atrium, into the right ventricle, and finally reach the pulmonary artery. Once in the artery, PAP is measured by a pressure transducer linked to the catheter (Holt and Callan, 2007). This PAP measurement is reflected on a monitor by a change in the pressure wave, which is induced by an increase in the diastolic pressure of the pulmonary artery over the diastolic pressure of the right ventricle. In an animal with normal health conditions, the mean PAP at altitudes between 1,500 and 2000 m should range from 34 to 44 mmHg. Cattle with evident symptoms of pulmonary hypertension can reach PAP measurements between 48 and 213 mmHg. These results establish that any animal with a PAP measurement above 50 mmHg should be evaluated to detect any cardiac murmurs or congenital defects. Generally, cattle over 12 months of age that report a PAP measurement below 41 mmHg at an altitude above 1,500 m are expected to maintain an adequate PAP at higher elevations and can be selected as breeding stock for high-altitude operations. Animals with PAP measurements ranging between 41 and 49 mmHg should be utilized with caution at high altitudes due to their performance unpredictability. Further, any cattle that scores a PAP measurement greater than 49 mmHg at any elevation has an increased risk of suffering high-altitude disease and should not be kept or bred at increased elevations (Holt and Callan, 2007). In addition, there several factors that affect PAP in cattle and contribute to its variation. Following performance of over 150,000 tests in cattle of multiple breeds, results indicate that no cattle are fully resistant to the negative effects of high-altitude disease. However, some breeds and pedigrees among breeds seem to have increased natural tolerance to this disease. In terms of age, increased variation of PAP is observed on animals under 12 months of age. Instead, it is recommended that PAP evaluations should be performed on animals at 16 months of age or older to increase consistency and accuracy of results. Further, environmental conditions may also have an effect on PAP evaluations. It has been reported that cold environmental temperatures can induce pulmonary hypertension in cattle, and in severe cases with temperatures below freezing point, PAP measurements can be increased by 25% to 55%, which may be caused by hypoventilation-induced hypoxia and increased pulmonary blood flow. Moreover, evidence indicates that susceptibility of cattle to hypoxia-induced pulmonary hypertension is a heritable trait (Holt and Callan, 2017). Based on these indications, Pauling et al. (2018) evaluated the relationship between PAP and elevation, by analyzing if PAP measurements recorded at moderate elevations (below 1,600 m) had a genetic correlation to PAP measurements recorded at high elevations (over 1,600 m). A substantial population of purebred Angus cattle was utilized to gather PAP and elevation data. The results obtained from this study indicated that PAP measurements collected from animals located in altitudes between 1,219 m and 1,600 m may be included as a correlated trait in a multi-trait genetic analysis to generate EPDs that can be utilized for selection of animals with increased tolerance to pulmonary hypertension (Pauling et al., 2018). In February 2019, the American Angus Association released a PAP EPD as an indicator of animals with lower risk of developing high-altitude disease. Lower PAP EPDs are more advantageous and indicate a capacity of generating progeny with lower PAP measures (Angus Newsroom, 2019).

Poole and Poole (2019) reported that ergot alkaloids present in endophyte-infected tall fescue negatively affected blood circulation to the reproductive organs and indicated arterial vasoconstriction to the ovary and uterus. This could limit transport of essential nutrients to these tissues and could potentially decrease sex steroid synthesis, follicular and luteal development, and dysregulate the estrous cycle, thus negatively impacting reproductive efficiency. Considering the vasoconstrictive similarities between high-altitude disease and fescue toxicosis, the possibility to utilize PAP as a phenotypic test to identify tolerant animals to fescue toxicosis arises. Furthermore, the availability of the PAP EPD increases the interest of this research due to the potential ability to predict genetic differences in beef herds and identify animals that would have a decreased risk of developing the symptoms of fescue toxicosis. Their ability to pass this genetic tolerance to their future offspring should be evaluated, which could provide tremendous opportunities of improvement for beef cattle producers in the Southeastern U.S.

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CHAPTER 2

Evaluation of the Effects of Endophyte-Infected Tall Fescue Consumption on the Pulmonary Arterial Pressure of Beef Cattle

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INTRODUCTION

Tall fescue (*Schedonorus arundinaceus* [Schreb.] Dumort) is the principal forage utilized by cattle producers in the Southeastern U.S. Its pastures have been widely planted by beef producers in this region due to its exceptional yields, even under challenging climatic and edaphic conditions, and its tolerance to high animal stocking rates. This superior performance ability is the result of a symbiotic relationship between the plant and the endophytic fungus (*Epichloë coenophiala*), which generates different ergot alkaloids that improve the plant resistance to pests and drought. Nonetheless, these chemical compounds are toxic to cattle and lead to different negative responses, commonly known as fescue toxicosis, which suppress their growth and performance (Strickland et al., 2011). It has been recently estimated that the negative economic impact generated by this disease accounts for approximately $2 billion in losses per year (Kallenbach, 2015).

More specifically, among the detrimental symptoms induced by fescue toxicosis are decreased weight gain and growth, poor reproductive efficiency, reduced milk production, vasoconstriction, suppressed levels of circulatory hormones, and increased susceptibility to heat stress due to retained winter hair coats (Klotz, 2015). Many of these symptoms are linked to the disruption of endocrine and ovarian functions, especially affecting circulating prolactin and progesterone concentrations. Prolactin is a polypeptide hormone produced by the lactotroph cells in the anterior pituitary and mediated by dopamine, which is responsible for multiple relevant processes in the organism, such as milk production and hair coat growth and shedding (Paterson et al., 1995). Progesterone is a lipid hormone produced by the corpus luteum in the ovary, and its main functions are the maintenance of pregnancy and suppression of ovulation (Poole and Poole, 2019). Further, ergovaline and ergotamine, the most abundant ergot alkaloids present in tall fescue, are known to cause potent and sustained contractile responses in the vascular system which lead to a reduction in peripheral blood circulation and a lower heart rate in cattle (Aiken et al., 2007; Pesqueira et al., 2014; Poole et al., 2018).

Considering these detrimental effects caused by fescue toxicosis, different efforts have been made to identify more efficient management strategies. Recently, some studies have focused on investigating the genetic components of the disease with the intention of detecting tolerant subgroups of cattle that can transmit this resistance to the next generations. A couple of methods that have proven to be efficient to identify these tolerant animals are incorporating the use of phenotypic selection parameters and expected progeny differences (EPD) in the genetic management of cattle herds. The utilization of a hair coat shedding score to evaluate the ability of cattle grazing endophyte-infected tall fescue to shed their winter coats earlier in the spring has generated positive results. It has been found that this specific group of cows are less exposed to heat stress during the summer, wean heavier calves, and have superior overall performance when compared to late-shedding cows (Gray et al., 2011; Poole et al., 2020). Based on these successful outcomes and the moderate heritability of the hair shedding trait, a hair shedding EPD (HS EPD) was released by the American Angus Association (AAA) in 2022 to assist producers in identifying animals with superior hair shedding genetics within their herds and to improve their selection criteria for replacement females and breeding sires. Furthermore, another example of the successful implementation of EPDs for selection of tolerant animals is the use of the PAP EPD to reduce the negative consequences of high-altitude disease. In 2019, AAA released a PAP EPD to be utilized by cattle producers in regions of high altitude where oxygen concentrations in the air are reduced. This lack of oxygen causes pulmonary arterial vasoconstriction (which can be measured with pulmonary arterial pressure), which changes the normal blood flow pattern and adds stress to the cardiovascular system that can result in right-side cardiac failure and death of the animal in severe cases (Holt and Callan, 2007).

The similar vasoconstrictive effects between high-altitude disease and fescue toxicosis support the hypothesis that pulmonary arterial pressure could be utilized as a phenotypic test to identify animals with an increased fescue tolerance. The use of the PAP EPD could be implemented to potentially predict genetic differences that can aid in identifying cattle with a lower risk of developing fescue toxicosis following exposure to the ergot alkaloids. Therefore, the objective of this study was to examine the relationship between PAP, hematologic measurements, and common production parameters in cows grazing endophyte-infected fescue, as a means to identify animals that are highly susceptible or resistant to fescue toxicosis.

MATERIALS AND METHODS

This study was conducted at two locations in the piedmont region of North Carolina, the Butner Beef Cattle Field and Laboratory (BBCFL) (altitude: 143 MASL) near Bahama, NC, and the Upper Piedmont Research Station (UPRS) (altitude: 262 MASL) near Reidsville, NC. All animal procedures were approved by the North Carolina State University Institutional Animal Care and Use Committee (NCSU IACUC #22-160).

Animals and Treatment

Cow performance and forage data were collected from early April to early July 2022 (see experimental timeline in Figure 2.1). Pregnant purebred Angus cows (n=72) in an age range between two and four years at BBCFL were randomly divided into two groups to graze either endophyte-infected (EI) or novel-endophyte (EN) tall fescue pastures for 14 consecutive weeks. Purebred Angus cows (n=34) in the same age range and pregnancy status at UPRS grazed EI tall fescue exclusively throughout the experiment. Cows had access to water and minerals *ad libitum* during the entire study, as well as access to natural shade in the pastures they grazed. Cows conceived via synchronized artificial insemination or by natural service if artificial insemination was unsuccessful.

To evaluate the animal's physiological responses to consumption of ergot alkaloids, body weight (BW), body condition score (BCS; adapted from Richards et al., 1986), hair coat score (HCS; adapted from Olson et al., 2003), hair shedding score (HSS; adapted from Gray et al., 2011), rectal temperatures, and jugular blood samples were collected on a weekly basis throughout the experiment. Objective scores of BCS, HCS, and HSS were all collected by two trained evaluators to calculate an average score for every animal on any given week. Weekly body weights were recorded utilizing a digital livestock scale and were utilized to calculate average daily gain considering the difference between two body weight measurements within their respective week of collection. Blood samples were collected from each animal via jugular venipuncture using 20-gauge needles and sterile, additive-free 10.0 mL vacutainers and K2 EDTA 5.4 mg vacutainers to prevent blood clotting (Becton Dickinson, Franklin Lakes, NJ). Following collection, blood samples were stored in a cooler with ice and then transported to the laboratory for processing. Upon arrival, additive-free blood samples were centrifuged for 20 minutes at 2,500 Xg at 4°C to facilitate serum collection. Two serum samples were collected from each centrifuged tube to be stored in one glass dram vial and one plastic micro-centrifuge tube, respectively, at -20°C until analysis was conducted. Blood samples in K2 EDTA tubes were inverted gently to mix the blood and used to perform a complete blood count (CBC) test. Blood from each sample was transferred to heparinized microhematocrit tubes, which were sealed with a clay mixture to prevent outflow. Further, the microhematocrit tubes were centrifuged for 8 minutes at a maximum speed of 12,700 Xg. Following centrifuging, a micro-capillary reader (International Equipment Company, Needham Heights, MA) was utilized to quantify the hematocrit for each sample.

In addition, PAP measurements were collected every four weeks, commencing on the first week of the trial, following the procedure established by Holt and Callan (2007) (see experimental timeline in Figure 2.1). All cows at UPRS were included in the PAP measurements. At BBCFL, analyzing PAP for the entire population of cows utilized in this study was not feasible due to amount of time required to perform the procedure in each animal. Therefore, a reduced, randomized and representative group (n=18) of animals per treatment was assigned to be evaluated for PAP. To perform this procedure, the animal was secured within the chute with a moderate amount of squeeze to reduce body movement. A halter was utilized to secure the head and expose the lateral jugular furrow in the neck. After identifying the jugular area, the proximal lateral aspect was scrubbed with a 4% solution of chlorhexidine to remove contaminating agents and allowed to air dry prior to needle insertion. Pressure was applied to the jugular vein at the level of the thoracic inlet to induce blood flow resistance and cause jugular vein distension. Following sufficient exposure, the proximal jugular vein was punctured with a 12-gauge, 9 cm needle until a constant blood flow was obtained. The needle was safely threaded down the jugular leaving 1 cm of its distal portion to allow needle control. A polyethylene catheter (internal diameter 1.19 mm, external diameter 1.7 mm) was flushed with 0.9% NaCl solution (approximately 1 mL) and then passed through the needle into the jugular vein. The catheter tubing was frequently flushed to aid the movement as it was gently advanced down the jugular vein. The external end of the catheter was connected to a transducer via 3-way stopcocks after approximately 30-40 cm of the catheter had been passed into the jugular vein, and it was flushed with NaCl solution to assure no air had entered the system. The transducer was then placed at an equal level to the base of the animal’s heart, which is approximately caudal to the point of the elbow, and introduction of the catheter was then advanced to the distal jugular vein, where the first pressure was taken to evaluate catheter location. The pressure reading was obtained by observing pressure changes and characteristics of the pressure wavelengths on a patient monitor (Datascope Passport 2; Mindray North America, Mahwah, NJ), which allowed for accurate knowledge of the location of the end of the catheter. The catheter was then passed into the right atrium through the right atrioventricular valve and into the right ventricle of the heart, where a second pressure measurement was observed to assure correct location. The catheter was then advanced from the right ventricle through the pulmonary valve and into the main pulmonary artery. The catheter remained in this location until the pressure observed in the monitor was constant. Once constant wavelengths and pressure were verified, the mean, systolic and diastolic pressure values were recorded for each animal. After measurements were collected, the needle was slowly pulled back and removed from the animal, followed by removal of the catheter from the jugular vein. The halter was then removed from the head and the animal was released from the chute. The animals were monitored daily for signs of pain or distress for 72 hours following this procedure.

Temperature and Temperature Humidity Index (THI)

Ambient temperature and relative humidity values were imported from the online database of the environmental station of each location, property of the Environment and Climate Observing Network of North Carolina State University (NCSU ECONet, 2023), utilizing the mean air temperature and mean relative humidity data of the specific days that cattle performance data was collected. The temperature-humidity index (THI, Buffington et al., 1977) was calculated to describe environmental conditions that the animals experienced during the collection periods. The THI was calculated using the following formula:

$$THI = T(°F) – [0.55 – (0.55 * RH / 100) * (T(°F) – 58)]$$

where T(°F) represents ambient temperature in °F and RH represents relative humidity.

Forage Measurements

Animals at UPRS grazed exclusively on endophyte-infected pastures, whereas animals at BBCFL grazed pastures known to be either endophyte-infected (EI) or novel-endophyte (EN) tall fescue, depending on group designation. Cattle were rotationally grazed depending on forage availability at each location among specific pastures to ensure sufficient forage availability and appropriate forage management. Prior to cattle being relocated to a new pasture, forage samples were collected from 10 random locations in each pasture by clipping an approximate 20- by 30-cm rectangle to 5 cm height, and three sets of composite samples taken from each pasture were stored in resealable plastic bags and placed in a cooler with ice to be transported to the laboratory. Upon arrival to the laboratory, all composite samples were stored in a walk-in refrigerated room at -18°C until further analyses were conducted. Nutrient quality composite samples were submitted to be analyzed for nutrient content, and the results obtained from the laboratory were averaged by experimental period (North Carolina Department of Agriculture – Food and Drug Protection Division Laboratory, Raleigh, NC; Table 2.1) Species composite samples were further evaluated in the laboratory by trained technicians to identify forage species present within the sample, and to separate tall fescue from other species to calculate percent of fescue in each sample and results averaged by experiment period (Table 2.2). Moreover, the tall fescue samples obtained after separation were freeze-dried in a general-purpose freeze drier (VirTis-ATS, Warminster, PA), ground in a Cyclotec 1093 sample mill (Foss Tecator, Hilleroed, Denmark) with a 1-mm particle screen, combined into composite samples according to their respective experiment period, and submitted to a laboratory for ergot alkaloid analysis (Veterinary Medical Diagnostic Laboratory, University of Missouri, Columbia, MO) to evaluate alkaloid type and load (Table 2.3) in the different pastures that cattle grazed during this project.

Serum Progesterone Assay and Analysis

Serum progesterone concentrations were analyzed for both locations and groups of cows at week 1, 3, 5, 7, 9, 11, and 13; which represent a bi-weekly measurement during the complete period of data collection. Concentrations were determined by a commercially available radioimmunoassay, Immuchem® Coated Tube Progesterone I^{125} RIA kit (MP Biomedicals, Costa Mesa, CA) and the Cobra II Auto Gamma counter (Packard Instrument Company, Inc., Meriden, CT). Concentrations were reported in ng per mL. The inter-assay CV was 1.39% and the intra-assay CV was 1.31%.

Statistical Analysis

Data were analyzed using the MIXED procedure of SAS 9.3 (SAS Inst. Inc., Cary, NC, 1996) with repeated measures. Individual animal was utilized as the experimental unit and the model for pulmonary arterial pressure, average daily gain, body condition scores, rectal temperatures, hair coat scores, hair shedding scores, progesterone concentrations, pregnancy status and temperature and humidity index included age of the animal, treatment (Endophyte-infected vs. Novel-endophyte), location (UPRS vs. BBCFL), and time (Weeks 1-14) (week dependent on model). Results were recorded as least square means ± SEM, where statistical significance was determined at $P \leq 0.05$ and statistical tendency at $0.05 \leq P \leq 0.10$.

RESULTS AND DISCUSSION

Cow Hemodynamics and Hematology

Pulmonary Arterial Pressure. Arterial pressure in the organism is influenced by the cardiac output, arterial elasticity, and peripheral vascular resistance. It can be regulated and affected by multiple mechanisms and factors. Ergot alkaloid consumption can affect the cardiovascular system by decreasing the heart rate and altering the vascular tone, which consequently may increase vasoconstriction and limit blood flow to different tissue and organs of the animal body (Strickland et al., 2011). For instance, reductions in blood flow rate and caudal artery luminal area were reported in heifers consuming a concentrate diet which contained endophyte-infected tall fescue seed (Aiken et al., 2007). Furthermore, pulmonary arterial pressure in cattle can also be affected by a decrease in oxygen concentration in the air, usually experienced as altitude increases, which causes arterial vasoconstriction and triggers high-altitude disease (Holt and Callan, 2007). Differences were found in animal PAP ($P<0.0001$) by location and treatment. Figure 2.2 indicates UPRS cows had a significantly lower mean PAP values (27.8±0.45 mmHg) than the BBCFL (EI) (31.5±0.61 mmHg) and BBCFL (EN) (36.4±0.62 mmHg) cows. Differences ($P=0.0002$) were also observed when analyzing mean PAP values over time. Figure 2.3 shows PAP by Measurement X Treatment: UPRS cows had lower mean PAP values vs. BBCFL cows throughout the study; BBCFL (EI) cows had lower mean PAP values vs. BBCFL (EN) cows throughout the study. Moreover, differences in mean PAP values ($P=0.0199$) were also observed when analyzing an interaction between treatment and BCS. Figure 2.4 shows PAP by Treatment X BCS: BBCFL (EN) cows reported higher PAP mean values for BCS 4, 5, 6, and 7, whereas no significant differences were observed between UPRS and BBCFL (EI) treatment groups in all BCS categories except 5. UPRS cows did not report a BCS of 3 throughout the study, whereas both BBCFL groups had no differences in the BCS 3 category. The UPRS cows had the lowest mean PAP values in all measurements in spite of being exposed to the greatest concentration of ergovaline (Table 2.3) during the study. Among the BBCFL groups, the cattle group that grazed on endophyte-infected pastures showed lower mean PAP values than the group grazing on novel-endophyte tall fescue pastures throughout the study. In addition, as the ergovaline concentration increased in the pastures where BBCFL (EI) cows grazed towards the last term of the study, their respective mean PAP values tended to decrease from 34.6±0.95 mmHg to 29.2±0.95 mmHg (Figure 2.5). These results suggest that ergovaline may have a lessening effect on mean PAP values, and that this effect may be proportional to the amount of ergovaline that the animal is exposed to. Further, the changes observed in BBCFL (EI) cows indicate that even moderate concentrations of ergovaline in tall fescue can alter the mean PAP values. Previous studies have demonstrated that blood flow to peripheral tissue and internal organs can be reduced following consumption of ergot alkaloids (Rhodes et al., 1991), and arterial vasoconstriction can cause reductions in cattle heart rate after initial intake of an alkaloid-infected diet (Aiken et al., 2007). PAP measurements are more frequently performed in regions located at high altitudes, especially over 1,200 MASL, to identify cattle with increased tolerance to high-altitude disease. At high elevations, a normal mean PAP is estimated to be between 34 and 44 mmHg, a range that was only attained by the BBCFL (EN) group of cows. From the perspective of this study, an effect of altitude on mean PAP values is disregarded due to the considerably lower elevations found at both research stations. Furthermore, differences were observed in mean PAP values of cows with different BCS among treatments. As BCS increased, BBCFL (EN) cows had higher mean PAP values.

However, no differences were identified in mean PAP values as BCS increased within each group of cows, indicating there is no direct effect of BCS on PAP.

Hematocrit. Blood is a specialized corporal fluid composed of plasma, erythrocytes, leukocytes, and platelets. It plays a fundamental role in maintaining homeostasis, which includes transporting oxygen and nutrients to lungs and tissue, regulating body temperature, forming blood clots to prevent excessive loss of blood, transporting cells and antibodies to combat infectious agents, and carrying waste products to the liver and kidneys for filtering and removal of the body (American Society of Hematology, n.d.). More specifically, bovine blood can be fractioned into plasma (65%) and cellular mass (35%), and these components are estimated to be made up of 80.9% water, 17.3% protein, 0.23% fat, 0.07% carbohydrates, and 0.62% minerals (Duarte et al., 1999). In mature, healthy animals with an adequate plane of nutrition, the total blood volume is generally estimated to be 6 to 8% of the body weight (WVU IACUC, 2020). One of the consequences experienced by cattle exposed to the ergot alkaloids present in tall fescue is vasoconstriction of blood vessels, which limits blood flow in the peripheral vascular system and leads to several other negative effects (Strickland et al., 2011). Among the multiple components of blood, erythrocytes are the most abundant cell, accounting for approximately 40% of its total volume. These cells have an average diameter of 5-6 µm in cattle, and its main function is to transport the oxygen that bounds to hemoglobin to the different tissues and organs around the body. When blood samples are analyzed, the percentage of the entire blood volume that is composed of erythrocytes is called hematocrit. Under specific conditions of poor nutrition and diseases like anemia, parameters such as hematocrit, red blood cell count, and hemoglobin will be decreased. In contrast, under specific conditions such as hypoxia caused by high-altitude or cardio-pulmonary diseases, or polycythemia caused by dehydration, those same parameters will be increased (Roland et al., 2014). Differences ($P<0.0001$) were observed in the animal hematocrit by location and treatment in this study. As shown in Figure 2.6, UPRS cows had higher hematocrit percentages (31.1±0.16%) when compared to both BBCFL (EI) (29.7±0.18%) and BBCFL (EN) (29.3±0.18%). Between the two groups at BBCFL, no differences ($P=0.1159$) were observed. Further, hematocrit was also different ($P<0.0001$) by treatment over time. Figure 2.7 shows Hematocrit by Treatment over time, where UPRS cows reported higher hematocrit percentages compared to both BBCFL groups during specific terms of the study. However, no differences ($P=0.1159$) were observed among BBCFL groups. In addition, hematocrit was also different ($P<0.0001$) when analyzed by age of cows. Figure 2.8 summarizes Hematocrit by Age, where four-year old cows had higher ($P<0.0001$) hematocrit percentages (31.9±0.3%) vs. two- and three-year old cows (29.3±0.12% and 29±0.15%, respectively, whilst no differences ($P=0.1716$) were observed between two- and three-year old cows. However, the greater hematocrit results from UPRS cows cannot be associated directly to an effect of the higher concentrations of ergovaline present in the pastures of this location, as different results have been previously reported. Alfaro et al. (2021) performed a study that analyzed the complete blood cell count on offspring born to dams that were genetically evaluated using the T-snip test for resistance to fescue toxicosis, which were exposed to fescue toxicity and rumen-protected niacin supplementation as a potential alleviator for alkaloid-induced vasoconstriction. The results showed there was a time effect for hematocrit, hemoglobin, and erythrocytes, which caused a reduction in concentrations of these parameters that was attributed exclusively to the administration of endophyte-infected tall fescue seeds on the experimental diet. Consequently, the authors declared that the hematocrit percentages indicated that the offspring were not dehydrated even though the experiment was performed under heat conditions during the summer months (Alfaro et al., 2021). The reference interval for hematocrit in adult bovine may vary from 21% to 38% , and generally beef breeds will have higher hematocrit values than dairy breeds, whereas non-lactating cows will have higher hematocrit values than lactating cows (Roland et al., 2014). Based on these parameters, all of the cows within the population had normal hematocrit levels throughout the study. Nonetheless, considering that over 80% of the blood composition is water, and elevated levels of hematocrit are associated to dehydration, future analyses focusing on water intake and hematology of cattle exposed to the ergot alkaloids present in tall fescue could provide a better understanding of this matter.

Cow Performance

Performance Parameters. Multiple studies have demonstrated the detrimental effects of fescue toxicosis in beef cattle performance (Bacon et al., 1977; Aiken at al., 2011; Strickland et al., 2011; Kallenbach, 2015; Poole et al., 2020). The severity of this disease can be determined by evaluating different performance parameters, such as body weight (BW), average daily gain (ADG), and body condition scores (BCS). Differences ($P<0.0001$) were found in animal BW by treatment and location. Figure 2.9 shows Body Weight by Treatment, where UPRS cows had heavier body weights (491.0±2.5 kg) then the BBCFL (EI) (472.7±2.4 kg) and BBCFL (EN) (479.1±2.5 kg) cows. The BBCFL (EI) cows tended to have lighter weights then BBCFL (EN) cows. Further, BW was also different ($P<0.0001$) when analyzed by age of cows. Figure 2.10 shows BW by Age, where BW increased proportionally with age, as four-year old cows had the heaviest weights (560.5±4.6 kg) among the age groups, whilst three-year old cows reported heavier weights (479.9±2.3 kg) than two-year old cows (467.8±1.9 kg). In contrast, no differences ($P=0.9297$) in BW were observed between treatments and location over time (Figure 2.11). The ADG and BCS were also evaluated utilizing the same format as forage samples, with the objective of identifying potential effects of forage nutritional values and ergot alkaloid concentrations on BW and BCS. Differences were observed when analyzing ADG by location and treatment over specific periods of time and comparing them to the entire study, indicating that the BBCFL (EN) group of cows tended ($P=0.0576$) to have higher ADG during periods 2, 3, and entire study (Figure 2.12). Comparably, there were differences ($P<0.0001$) between BCS in treatment by location. As Figure 2.13 shows, UPRS cows had higher BCS (5.4 ± 0.1) than both BBCFL (EI) and (EN) cows (4.9 ± 0.1). Differences in BCS were also observed in treatment by location over time. Figure 2.14 shows UPRS cows had significantly greater BCS than both BBCFL groups during the first half of the study. However, BBCFL (EI) and (EN) cows significantly increased their BCS as time progressed, while UPRS cows decreased their BCS below BBCFL groups towards the end of the study. The differences in BW and BCS of cows between locations are associated to the forage quality results, as pastures at both locations showed reductions in their nutritional value as the study progressed, and the variations observed in values like crude protein and TDN can impact negatively on the animal's weight gain. In addition, these differences may also be partially attributed to distinct selection strategies that impact on phenotypic variation within the herds and contrasts in feed management strategies utilized throughout the year at both research stations. Within the same location, the lessening tendency observed in BW of BBCFL (EI) cows when compared to (EN) cows may be attributed to the effects of ergot alkaloids present in the tall fescue pastures where (EI) cows grazed throughout the study. In terms of BW by age, the observed differences may be associated to the specific age range of the animals used in this study, as it has been demonstrated that cows can still increase their weight following the typical growth curve of beef cattle (Tisch, 2006), and it may also be affected by the physiological processes related to pregnancy development.

Moreover, the analysis of BW and BCS by treatment over time showed that UPRS cows had heavier weights and higher BCS when compared to both BBCFL groups in the first half of the study. During the second half, both BBCFL groups reported increases in weights while UPRS cows showed a plateau behavior in their weights and a decrease in BCS over the same period. These results correlate to the performance observed in the ADG analysis, which denoted higher gains for UPRS cows during Period 1 and higher gains for BBCFL (EN) cows in Periods 2 and 3. These results may be related to the greater nutritional value of UPRS pastures during Period 1 (Table 2.1), while the differences in ADG observed in Periods 2, 3, and in the Entire Study between BBCFL (EN) cows vs. the endophyte-exposed groups at both locations may be attributed to the negative effects of ergot alkaloid consumption. Further, UPRS cows tended to have lower ADG than BBCFL (EI) in Periods 2 and 3, which may be related to the observed decrease in BCS during the same period and might be explained by the higher concentrations of ergovaline present in UPRS pastures (Table 2.3). Similarly, Coffey et al. (2001) and Caldwell et al. (2013) reported direct negative effects on animal BW, BCS, and ADG when endophyte-infection rates increased in tall fescue pastures.

Temperature and Humidity Parameters. Among the multiple negative effects induced by fescue toxicosis, impaired thermoregulation leads to consequences such as increased rectal temperature and respiration rate, which in conjunction with decreased feed intake and weight gains can depress cattle productivity. It is common that cattle exposed to endophyte-infected fescue register rectal temperatures within the fever range. Fescue toxicosis severity can also be increased by environmental factors like ambient temperature and relative humidity (Eisemann et al., 2014). As endophyte-infected tall fescue finalizes the first growth period during late spring and early summer, environmental temperatures in regions of the Fescue Belt can rise to a point of provoking heat stress in cattle. It has been estimated that heat stress-related conditions in beef cattle cause an annual economic loss of $2.4 billion in the U.S agricultural sector (Mote et al., 2020). In this regard, it becomes important to understand how these mechanisms interact with each other to find potential solutions to these challenges. One of the parameters to be considered is the Temperature Humidity Index (THI), which relates the combined effects of dry-bulb temperatures and humidity to animal comfort and performance (Buffington, 1977). The calculation of this index has allowed scientists to elaborate a chart that aids on determining the levels of risk that cattle may be exposed to during seasons with high temperatures and improve strategic planning of cattle movements and other related activities. This chart defines the normal THI range for cattle to be below 75 units, an alert THI between 75 and 78 units, a danger THI between 79 and 83 units, and an emergency THI equal to or greater than 84 units (UNL Beef, 2014). Differences ($P<0.0001$) were detected in rectal temperatures of cows utilized in this study over time. Figure 2.15 shows rectal temperatures significantly varied between locations continually throughout the study. UPRS cows reported higher rectal temperatures (39.01±0.04℃) when compared to BBCFL (EI) and BBCFL (EN) cows (38.95±0.04℃ and 38.93±0.04℃, respectively). In terms of THI, significant differences ($P<0.0001$) were observed between locations over time. Figure 2.16 shows that both groups of cows at BBCFL were exposed to a higher THI (75.42±0.09 THI units) when compared to UPRS cows (73.36±0.09 THI units). The fluctuating behavior observed in rectal temperatures throughout the study may be influenced by several factors rather than being attributed exclusively to fescue toxicosis. These variables include the specific environmental conditions that were experienced by the animal at the time of measurement and the physical activity performed inside the holding pens before getting to the chute. In detail, the rectal temperatures of UPRS cows fluctuated between the normal body temperature (38.5℃) and the fever threshold (39.5℃) established for cattle (Burfeind et al., 2012), despite being exposed to the higher concentration of ergot alkaloids; whereas BBCFL (EI) cows reported higher rectal temperatures than UPRS cows during the second half of the study, in spite of being exposed to a decreased concentration of ergot alkaloids. This might be related to the specific THI that each group of cows experienced throughout the study, in addition to other variables related to location. During the first half of the study, UPRS cows remained in the normal THI range and were not exposed to higher ranges that could cause heat stress. In contrast, both groups at BBCFL were exposed to the alert THI ranges during this same period of time. In the last half of the study, as it transitioned from late spring to early summer, all groups of cows at both locations reached the alert, danger, and emergency THI ranges. Interestingly, the rectal temperatures of BBCFL (EN) cows remained within an acceptable range during the last half of the study, indicating an adequate thermoregulation despite the extreme THI conditions. This ability may be related to the reduced exposure to ergot alkaloids present in endophyte-infected tall fescue. In contrast, both groups of cows that were exposed to endophyte-infected pastures reported increases in the rectal temperatures each time the THI index exceeded the alert THI range. Ergot alkaloid impact on thermoregulation also negatively affects other parameters in cattle, such as respiration rate, feed intake and efficiency, which ultimately decreases cattle productivity and efficiency (Caldwell et al., 2013; Ball et al., 2015).

Hair Shedding Ability. Winter hair coat retention is one of the most evident symptoms of fescue toxicosis, which increases the animal susceptibility to heat stress and causes numerous negative consequences in cattle (Porter and Thompson, 1992; McClanahan et al., 2008). Additionally, it has been determined that cattle with increased capacity to shed winter hair coats earlier in the spring are more productive, and also are able to pass this trait to their offspring

(Gray et al., 2011). In this study, hair coat scores (HCS) and hair shedding scores (HSS) were evaluated to determine the rate of shedding for each animal. Differences were reported in HCS by treatment and location ($P=0.0006$). Figure 2.17 shows that BBCFL (EN) cows had lower scores (2.2±0.2) than BBCFL (EI) and UPRS cows (3.2±0.2 and 2.9±0.2, respectively). No significant differences ($P=0.2551$) were observed between BBCFL (EI) and UPRS cows. Differences were also observed in HCS between location and treatment over time ($P<0.0001$). Figure 2.18 describes that BBCFL (EN) cows showed a greater capacity than BBCFL (EI) and UPRS cows to reduce the hair coat scores as the study progressed, whereas BBCFL (EI) and UPRS groups tended to show similar results. Comparably, HSS results indicated significant differences in treatment by location ($P=0.0026$). Figure 2.19 demonstrates that BBCFL (EN) cows showed lower shedding scores (2.4±0.2) than BBCFL (EI) cows (3.3±0.2), whilst a tendency ($P=0.0636$) was detected between UPRS cows (3.0±0.3) and the other two groups. In addition, differences were identified in HSS between location and treatment over time ($P<0.0001$). Figure 2.20 describes that BBCFL (EN) cows showed a greater capacity than BBCFL (EI) and UPRS cows to shed the hair coat as the study progressed, whereas BBCFL (EI) and UPRS groups showed similar results. The differences observed between cows that grazed on novel-endophyte pastures and those grazing on endophyte-infected pastures indicate an impact of ergot alkaloids on that characteristic retention of winter hair coats induced by fescue toxicosis. Moreover, those differences were confirmed when analyzing both HCS and HSS over time, as both groups of cows exposed to endophyte-infected pastures reported similar scores throughout the study regardless of location, whereas the BBCFL (EN) group demonstrated an increased ability to shed their winter hair coats. This advantage may explain the greater ability of BBCFL (EN) cows to maintain relatively normal rectal temperatures despite of being exposed to emergency THI during the second half of the study. This group also had increased ADG observed over time in these animals when compared to BBCFL (EI) and UPRS cows, which corresponds to results reported by other similar studies (Watson et al., 2004; Poole et al., 2020).

Hormone Profile

Progesterone Concentration. Fescue toxicosis triggers various reproductive alterations, including altered cyclicity and suppressed hormone production which can lead to decreased pregnancy rates and calf development. Among the affected hormones, serum progesterone (P4) concentrations are reduced in cows that graze on endophyte-infected pastures. P4 is the principal hormone produced by the corpus luteum, and is mainly responsible for ovulation suppression and maintenance of pregnancy (Poole and Poole, 2019). Differences ($P<0.0001$) were observed in concentrations of serum P4 between treatments and locations. Figure 2.21 shows that BBCFL (EN) cows had higher P4 concentrations (6.2±0.4 ng/mL) than BBCFL (EI) and UPRS cows (4.0±0.4 ng/mL and 3.4±0.4 ng/mL, respectively), whereas no differences ($P=0.2892$) were observed between both groups exposed to endophyte-infected pastures. Additionally, serum progesterone concentrations differed ($P<0.0001$) between treatments and location over time. Figure 2.22 describes that BBCFL (EN) cows had higher concentrations of P4 than BBCFL (EI) and UPRS cows as the study advanced, whereas BBCFL (EI) and UPRS cows reported comparable P4 concentrations throughout the study. The differences observed between BBCFL (EN) cows and both BBCFL (EI) and UPRS cows may be attributed to an effect of ergot alkaloid consumption. Moreover, the trendlines observed in Figure 2.21 also indicate a different pattern between both endophyte-exposed groups, with BBCFL (EI) cows showing a positive slope while UPRS cows reflect a negative slope. This contrast may be related to the higher ergovaline concentration reported in UPRS pastures when compared to the pastures grazed by BBCFL (EI) cows (Table 2.3). It has been reported that blood vessel vasoconstriction associated to ergot alkaloid consumption can reduce the diameter of the ovulatory follicle, which consequently decreases the luteal area and negatively affects P4 production (Poole et al., 2019). Similarly, Mahmood et al. (1994) reported reduced P4 concentrations and luteal dysfunction on heifers exposed to high concentrations of ergot alkaloids (Mahmood et al., 1994). Furthermore, the three groups of cows utilized in this study reported a significant reduction of P4 concentration in the last week (Figure 2.21). This decrease was most probably a consequence of heat stress, as all groups were exposed to increased THI during the last weeks of the study. Correspondingly, Burke et al. (2001) and Poole et al. (2019) demonstrated that heat stress aggravated the symptoms of fescue toxicosis and significantly decreased P4 concentrations in heifers consuming endophyte-infected tall fescue. Based on these results, as well as other parameters evaluated and described as part of this research, a novel approach to analyze the impact of ergot alkaloid consumption on PAP is established. The interaction between these two variables, which is demonstrated as inversely proportional by this study, could provide an unprecedented asset to incorporate into the strategies utilized by producers to manage fescue toxicosis in beef cattle.

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TABLES

Table 2.1. Nutritive Value (on a DM basis) of forage samples.

	UPRS (EI)[1]				BBCFL (EI)[2]				BBCFL (EN)[3]			
	P-1[4]	**P-2[5]**	**P-3[6]**	**ES[7]**	**P-1[4]**	**P-2[5]**	**P-3[6]**	**ES[7]**	**P-1[4]**	**P-2[5]**	**P-3[6]**	**ES[7]**
DM (%)	25.2	22.5	32.6	26.8	25.4	34.4	38.7	32.8	26.1	28.5	34.2	29.6
CP (%DM)	22.75	18.03	11.31	17.36	14.49	11.28	10.01	11.93	18.00	12.84	13.55	14.80
NDF (%DM)	52.4	59.3	67.2	59.6	57.7	64.6	67.5	63.3	56.8	61.5	59.9	59.4
ADF (%DM)	26.5	33.4	34.0	31.3	30.5	36.5	40.1	35.7	31.3	37.3	35.3	34.7
TDN (%DM)	76.2	69.7	69.6	71.8	72.7	67.4	64.9	68.3	72.1	67.2	68.3	69.2
Ash (%DM)	8.04	7.26	6.23	7.18	6.54	6.31	6.46	6.4	7.09	6.20	7.58	7.0
Ca (%DM)	0.420	0.450	0.350	0.407	0.310	0.345	0.350	0.335	0.380	0.440	0.460	0.427
P (%DM)	0.280	0.290	0.200	0.257	0.310	0.285	0.260	0.285	0.320	0.270	0.340	0.310
S (%DM)	0.300	0.260	0.190	0.250	0.190	0.170	0.170	0.177	0.220	0.195	0.250	0.222
Mg (%DM)	0.250	0.240	0.190	0.227	0.270	0.285	0.300	0.285	0.280	0.300	0.380	0.320
Na (%DM)	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.020	0.040	0.020
K (%DM)	2.540	2.620	2.000	2.387	2.140	1.750	1.670	1.853	1.970	2.005	2.060	2.012
Cu (ppm)	6.420	0.000	0.000	2.140	0.000	2.105	0.000	0.702	6.740	2.935	5.730	5.135
Fe (ppm)	78.85	0.00	0.00	26.3	0.00	32.47	69.34	33.94	0.00	0.00	60.43	20.14
Mn (ppm)	79.90	56.11	54.80	63.60	109.08	98.73	114.00	107.27	115.41	81.48	75.43	90.77
Zn (ppm)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

[1] UPRS (EI): Endophyte-infected tall fescue pastures located at Upper Piedmont Research Station, Reidsville, NC
[2] BBCFL (EI): Endophyte-infected tall fescue pastures located at Butner Beef Cattle Field Laboratory, Bahama, NC
[3] BBCFL (EN): Novel-endophyte tall fescue pastures located at Butner Beef Cattle Field Laboratory, Bahama, NC
[4] P-1: Period 1, using collected forage samples from weeks 1, 2, 3, 4 and 5
[5] P-2: Period 2, using collected forage samples from weeks 6, 7, 8, 9 and 10
[6] P-3: Period 3, using collected forage samples from weeks 11, 12, 13 and 14
[7] ES: Entire study, using average nutrient values from Periods 1, 2, and 3

Table 2.2. Prevalence of tall fescue in forage samples

	UPRS (EI)[1]				BBCFL (EI)[2]				BBCFL (EN)[3]			
	P-1[4]	**P-2[5]**	**P-3[6]**	**ES[7]**	**P-1[4]**	**P-2[5]**	**P-3[6]**	**ES[7]**	**P-1[4]**	**P-2[5]**	**P-3[6]**	**ES[7]**
Percent of tall fescue (%)	79.6	83.1	62.8	75.2	56.8	58.4	63.7	59.6	85.3	82.0	62.3	76.5

[1] UPRS (EI): Endophyte-infected tall fescue pastures located at Upper Piedmont Research Station, Reidsville, NC
[2] BBCFL (EI): Endophyte-infected tall fescue pastures located at Butner Beef Cattle Field Laboratory, Bahama, NC
[3] BBCFL (EN): Novel-endophyte tall fescue pastures located at Butner Beef Cattle Field Laboratory, Bahama, NC
[4] P-1: Period 1, using forage samples from weeks 1, 2, 3, 4 and 5
[5] P-2: Period 2, using forage samples from weeks 6, 7, 8, 9 and 10
[6] P-3: Period 3, using forage samples from weeks 11, 12, 13 and 14
[7] ES: Entire study, using average values from Periods 1, 2, and 3

Table 2.3. Ergot alkaloid infection levels in tall fescue samples

	UPRS (EI)[1]				BBCFL (EI)[2]				BBCFL (EN)[3]			
Ergot Alkaloids (ng/mL)	**P-1**[4]	**P-2**[5]	**P-3**[6]	**ES**[7]	**P-1**[4]	**P-2**[5]	**P-3**[6]	**ES**[7]	**P-1**[4]	**P-2**[5]	**P-3**[6]	**ES**[7]
Ergovaline	267	373	261	300	94	112	170	125	57	60	34	50
Ergosine	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D
Ergotamine	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D
Ergocornine	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D
Ergocryptine	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D
Ergocristine	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D	N.D
Ergot Total	< 25	< 25	< 25	< 25	< 25	< 25	< 25	< 25	< 25	< 25	< 25	< 25

[1] UPRS (EI): Endophyte-infected tall fescue pastures located at Upper Piedmont Research Station, Reidsville, NC
[2] BBCFL (EI): Endophyte-infected tall fescue pastures located at Butner Beef Cattle Field Laboratory, Bahama, NC
[3] BBCFL (EN): Novel-endophyte tall fescue pastures located at Butner Beef Cattle Field Laboratory, Bahama, NC
[4] P-1: Period 1, using tall fescue samples from weeks 1, 2, 3, 4 and 5
[5] P-2: Period 2, using tall fescue samples from weeks 6, 7, 8, 9 and 10
[6] P-3: Period 3, using tall fescue samples from weeks 11, 12, 13 and 14
[7] ES: Entire study, using average values from Periods 1, 2, and 3
N.D: Not detected

FIGURES

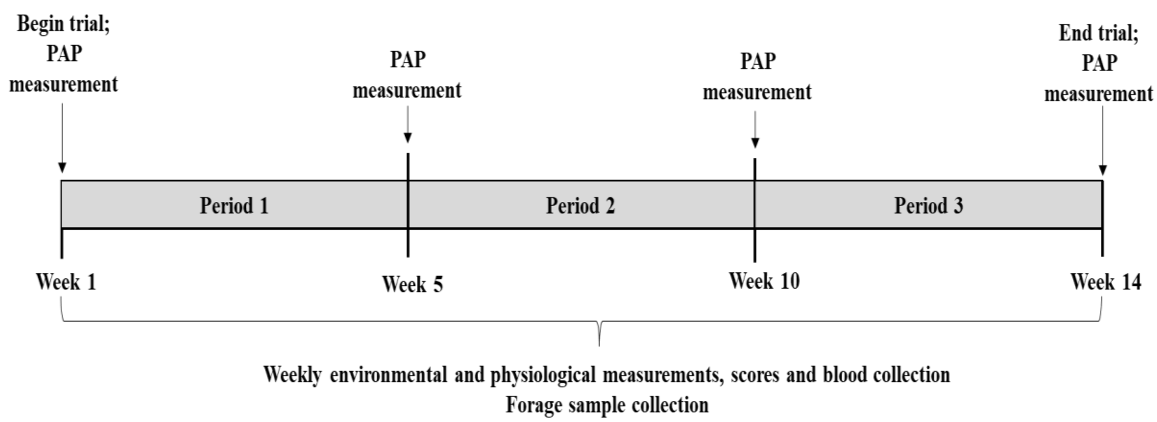

Figure 2.1: Experimental timeline used during phase of data collection from early-April to mid-July 2022.

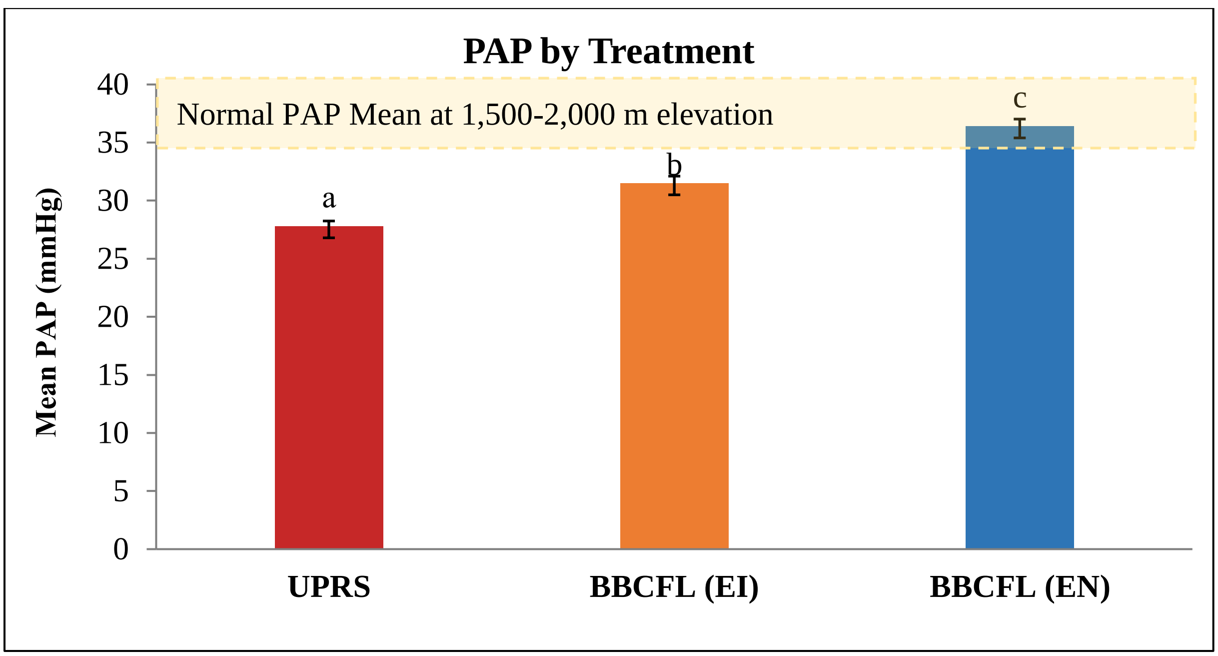

Figure 2.2: PAP by location and treatment: UPRS cows had lower PAP mean values (27.8 mm/Hg) vs. BBCFL (EI) and (EN) cows (31.5 mm/Hg and 36.4 mm/Hg, respectively). Within BBCFL groups, (EI) cows had lower PAP mean values vs. (EN) cows. Model was significant by treatment and location, (trt, loc P-values: P<0.0001; different letter superscripts indicate statistical difference).

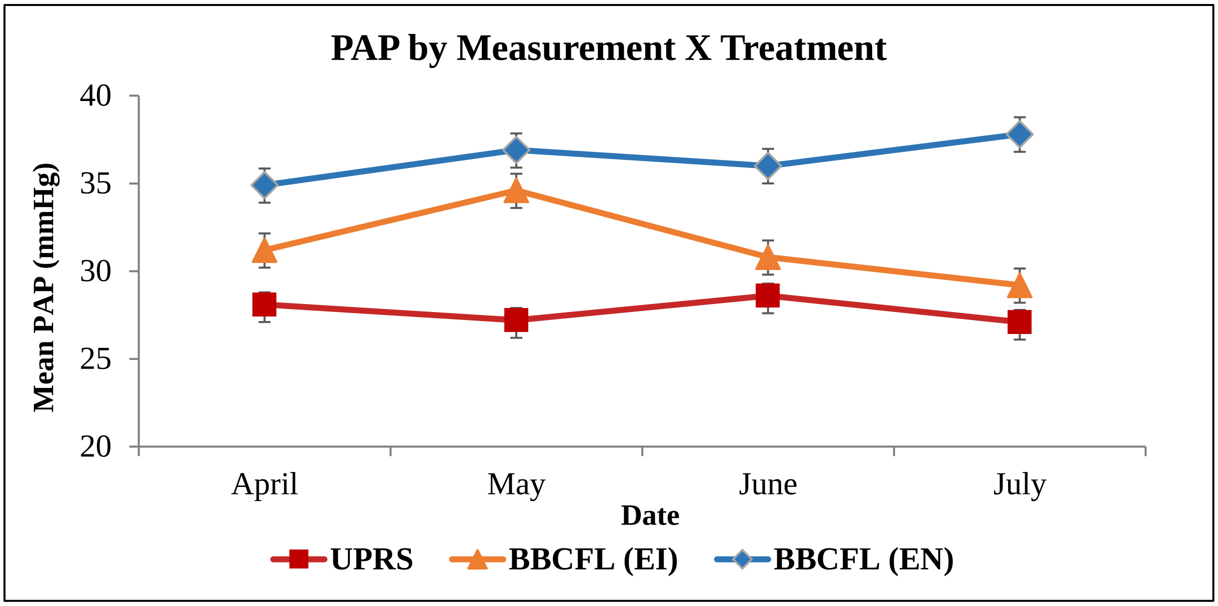

Figure 2.3: PAP by measurement and treatment over time: UPRS cows had lower PAP mean values vs. BBCFL cows throughout the study. Within BBCFL groups, (EI) cows had lower PAP mean values vs. (EN) cows throughout the study. Model was significant by treatment X location by date (Treatment X location by date P-value: P=0.0002).

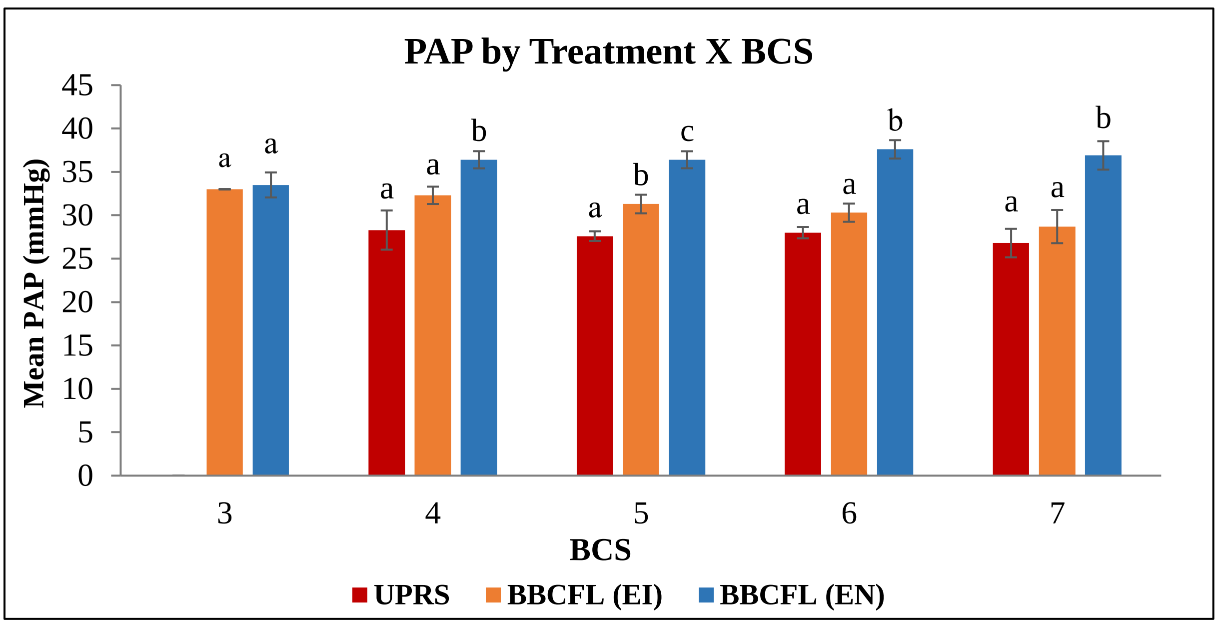

Figure 2.4: PAP by Treatment X BCS: BBCFL (EN) cows had higher PAP mean values for BCS 4, 5, 6, and 7. No significant differences were observed between UPRS and BBCFL (EI) groups in all BCS categories except 5. No cows at UPRS were reported to have a BCS 3 throughout the study. No differences were observed between BBCFL groups in BCS 3. Model was significant by treatment X BCS (Treatment X BCS, P=0.0199; different letter superscripts indicate statistical difference).

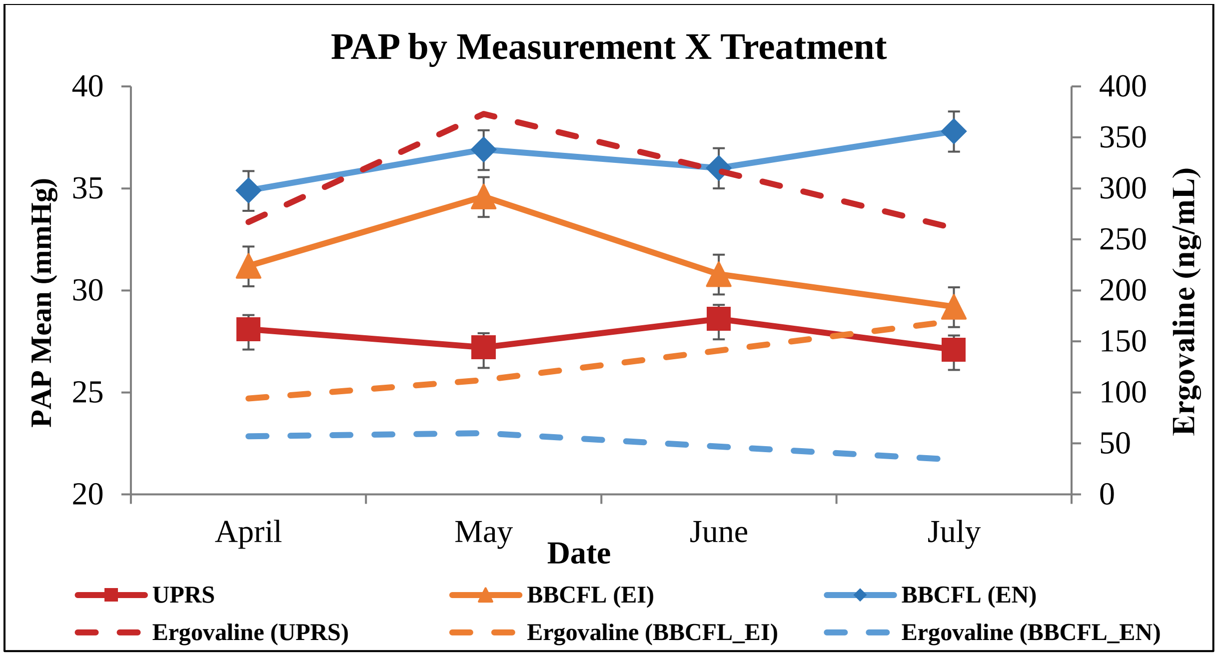

Figure 2.5: PAP by location and treatment and Ergovaline concentrations over time: Ergovaline concentrations demonstrated a lessening effect on mean PAP values throughout the study. Model was significant by treatment X location by date (treatment X location by date P-value: P=0.0002).

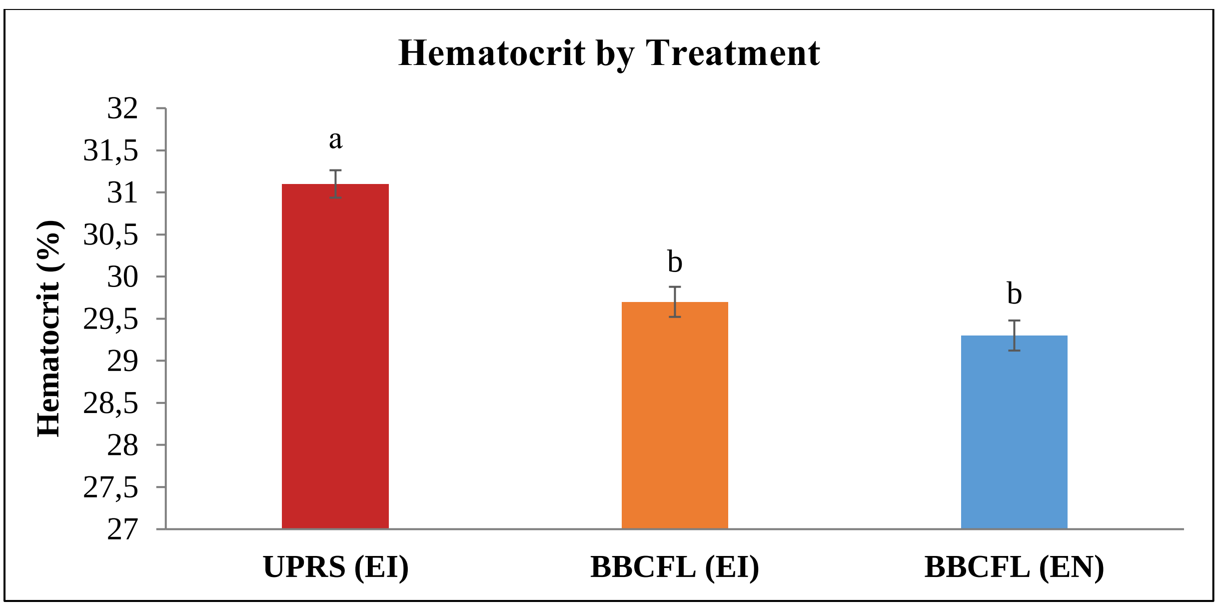

Figure 2.6: Hematocrit by Treatment: UPRS cows had higher hematocrit percentages (31.1) when compared to both BBCFL (EI) and (EN) groups (29.7 and 29.3, respectively). Between the two groups at BBCFL, no significant differences were observed. Model was significant by treatment, week, treatment X location (trt, week, trtXloc P-values: P<0.0001); different letter superscripts indicate statistical difference).

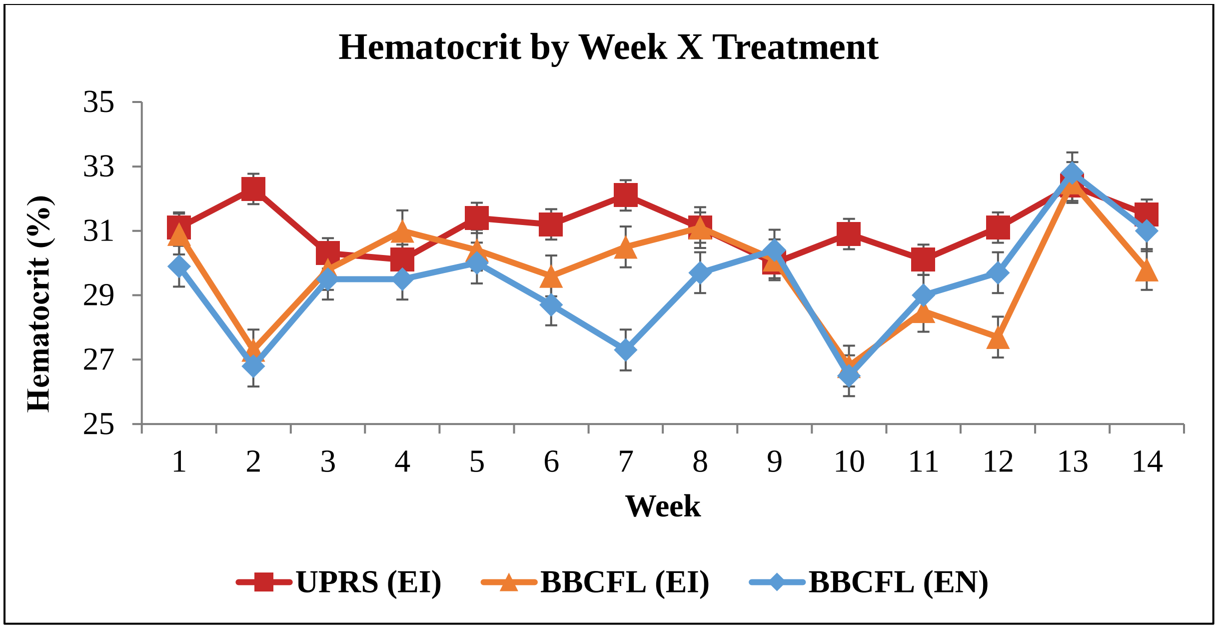

Figure 2.7: Hematocrit by Treatment (over time): UPRS cows reported higher hematocrit percentages vs. both BBCFL groups in some terms during the study; At BBCFL, no significant differences were observed among groups. Model was significant by treatment, week, treatment X location, and age (trt, week, trtXloc P-values: P<0.0001).

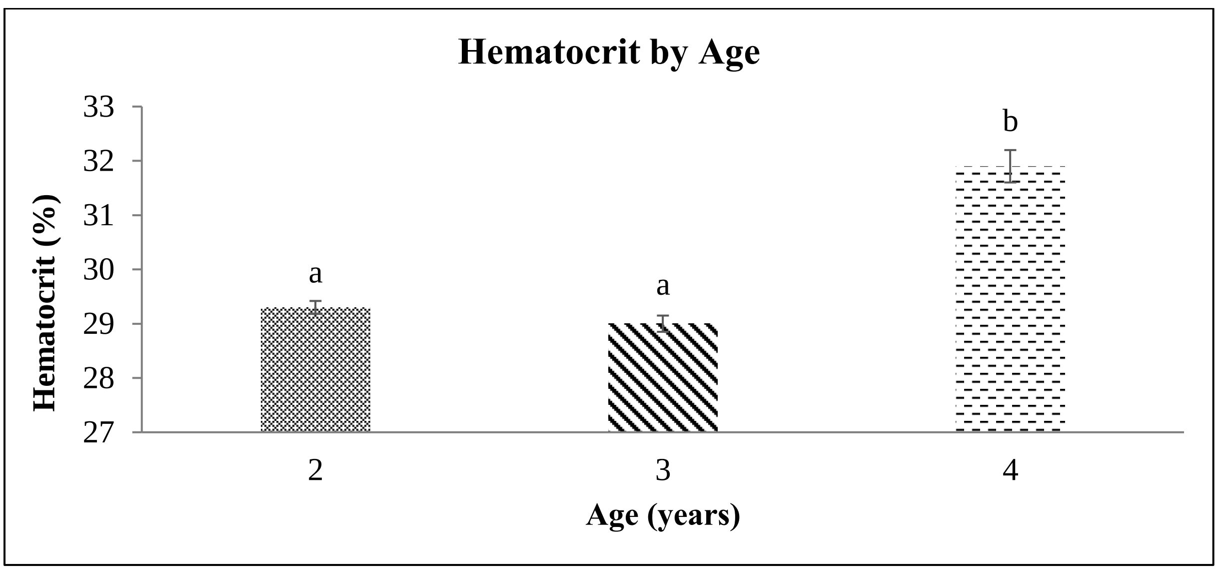

Figure 2.8: Hematocrit by Age: Four-year old cows had higher hematocrit percentages (31.9) vs. two- and three-year old cows (29.3 and 29, respectively). No differences were observed between two- and three-year old cows. Model was significant by age (P-value: P<0.0001).

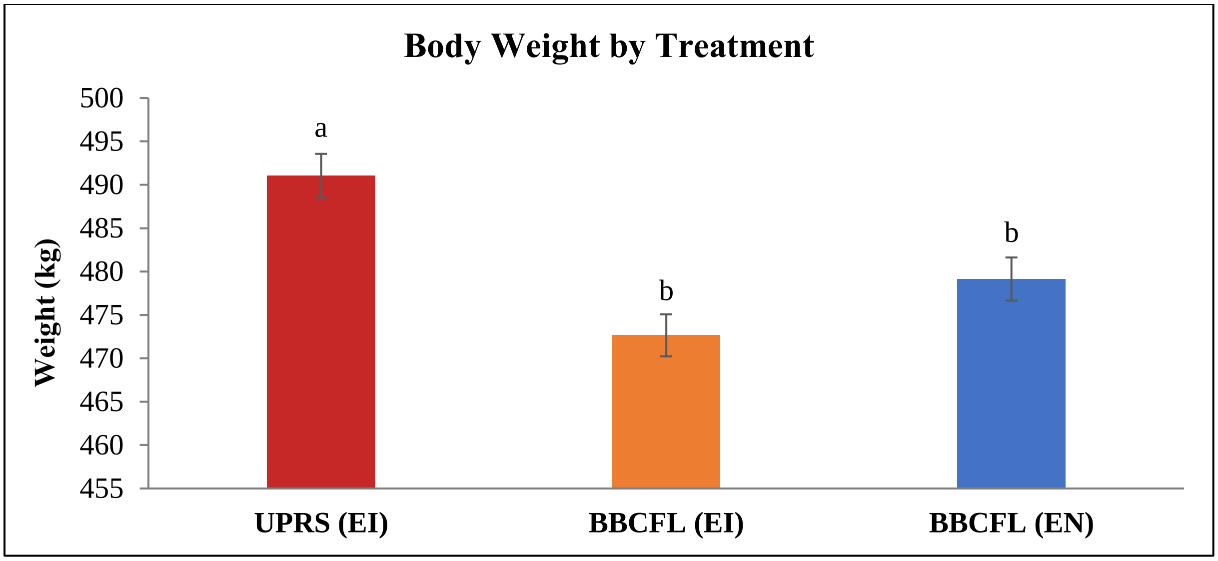

Figure 2.9: Body Weight by Treatment: UPRS cows had heavier body weights (491.04 kg) vs. BBCFL (EI) and (EN) groups (472.66 kg and 479.14 kg, respectively). Between the BBCFL groups, (EI) cows tended to have reduced weights vs. (EN) cows). Model was significant by treatment and location (trt, loc, P<0.0001; different letter superscripts indicate statistical difference; same letter superscripts indicate statistical tendency).

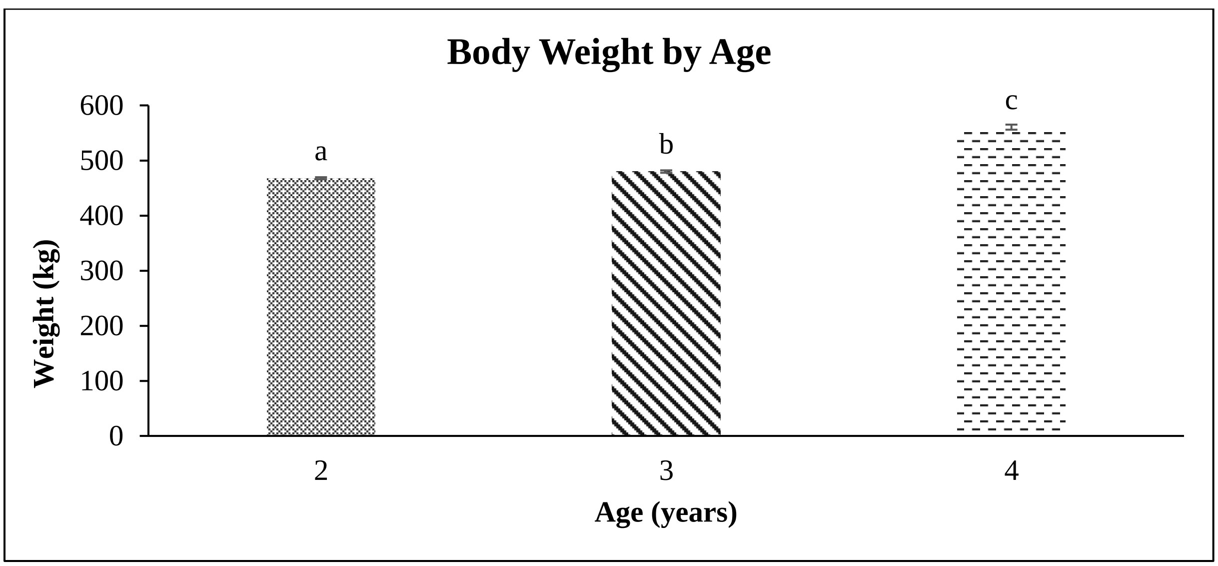

Figure 2.10: Body Weight by Age: Four-year old cows had heavier weights (560.48 kg) vs. three- and two-year old cows (479.88 kg and 467.76 kg, respectively). Two-year old cows reported the lowest weights. Model was significant by age (P<0.0001; different letter superscripts indicate statistical difference).

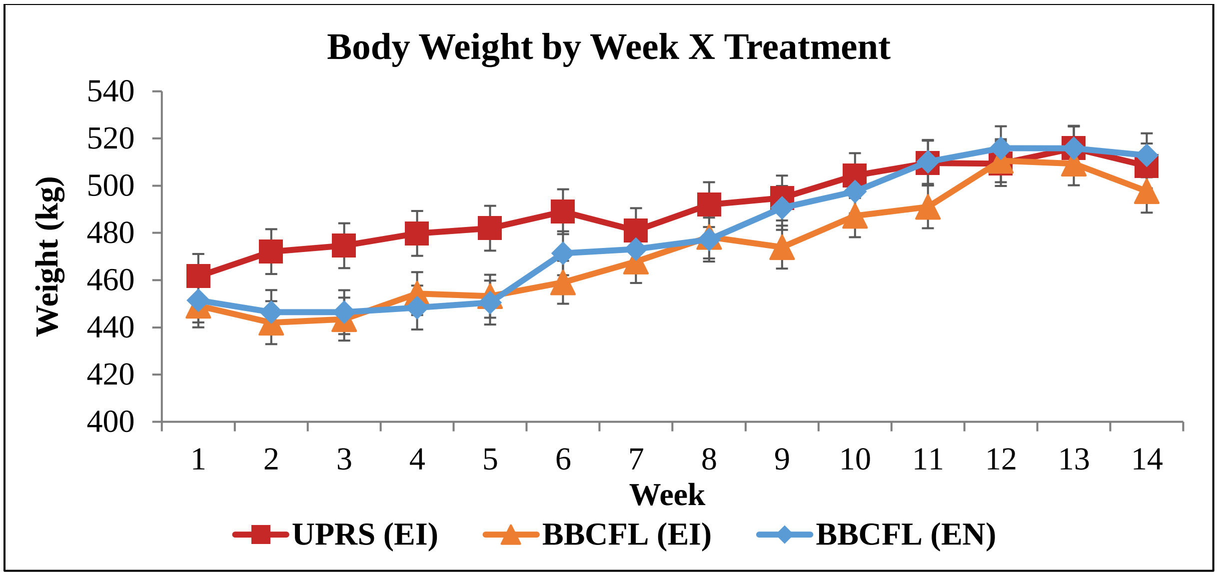

Figure 2.11: Body Weight by Treatment over time (weeks): UPRS showed higher body weights vs. both BBCFL groups in the first half of the study. However, no differences were observed between groups in the second half of the study. Model did not show significant differences in body weights by treatment and location over time (trtXweek P-value: P=0.9297)

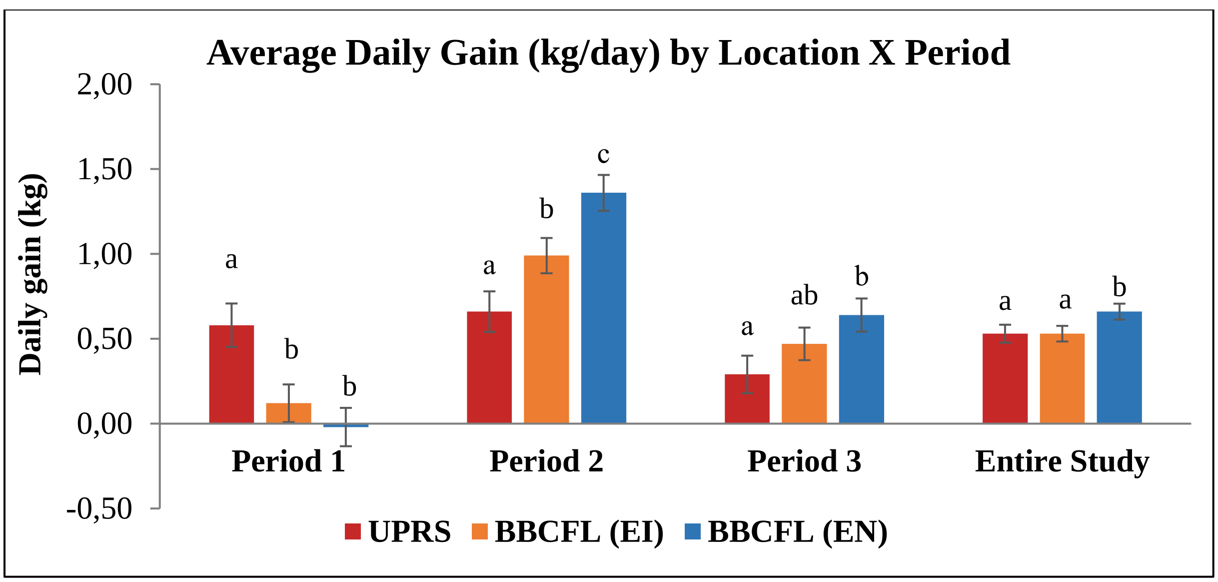

Figure 2.12: ADG by Location over time (Period 1, Period 2, Period 3, Entire Study): UPRS cows had higher weight gains during Period 1 than both BBCFL (EI) and BBCFL (EN) cows (trt, loc P=0.004). However, BBCFL (EN) cows had higher weight gains during Period 2 (trt, loc P=0.0042), Period 3 (trt, loc P=0.0374) and in the Entire study analysis (trt, loc P=0.0576; different letter superscripts indicate statistical difference within their respective period).

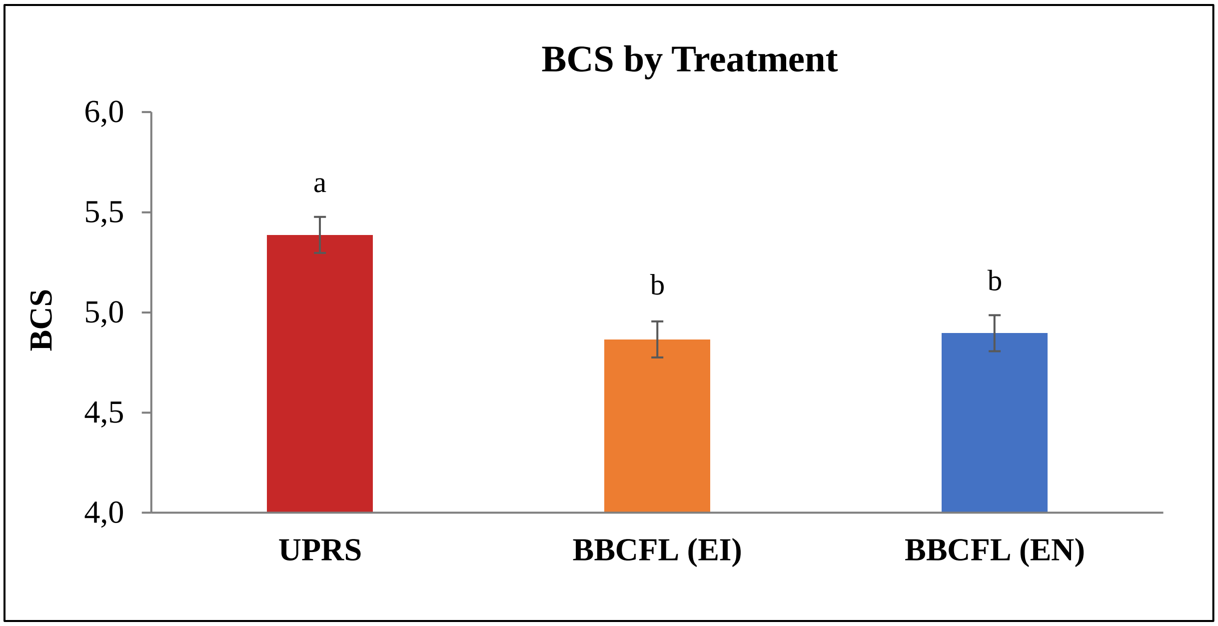

Figure 2.13: BCS by Treatment: UPRS cows had significantly higher BCS vs. both BBCFL (EI) and (EN) cows. Model was significant by treatment, location, and treatment by location (trt, loc, and trtXloc, P<0.0001; different letter superscripts indicate statistical difference).

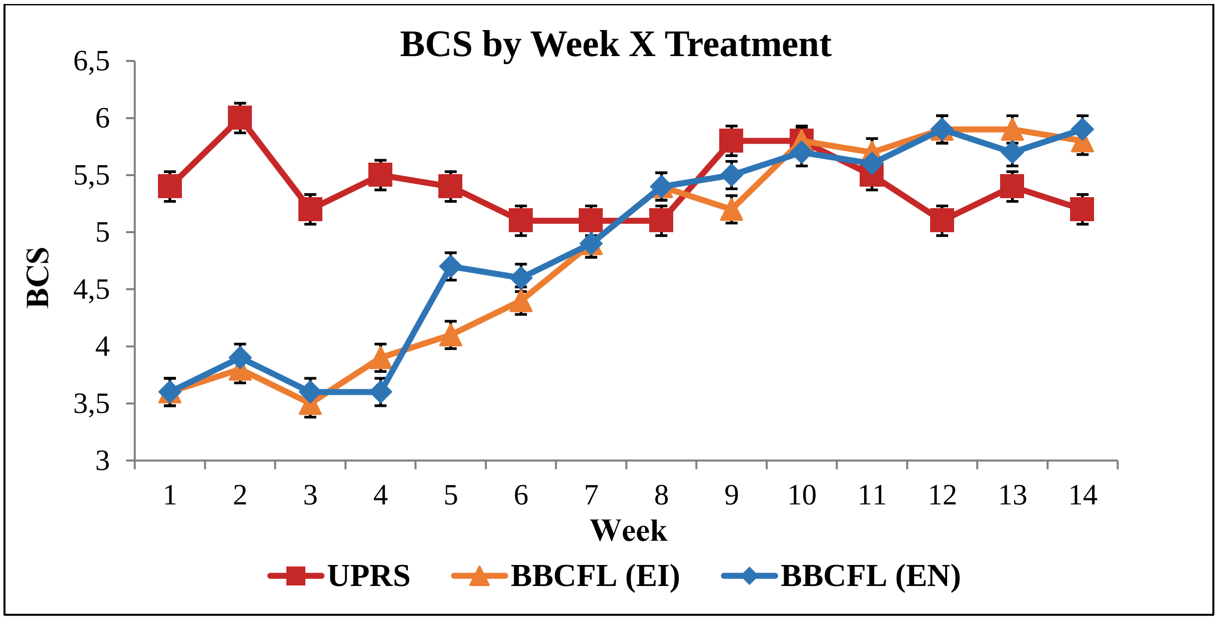

Figure 2.14: BCS by Treatment over time (weeks): UPRS cows had significantly greater BCS vs. both BBCFL groups during the first half of the study. However, BBCFL (EI) and (EN) cows significantly increased their BCS at a similar rate as time progressed, while UPRS cows decreased their BCS below BBCFL groups towards the end of the study. Model was significant by treatment, location, week and treatment by location (trt, loc, week, and trtXloc P-values: P<0.0001).

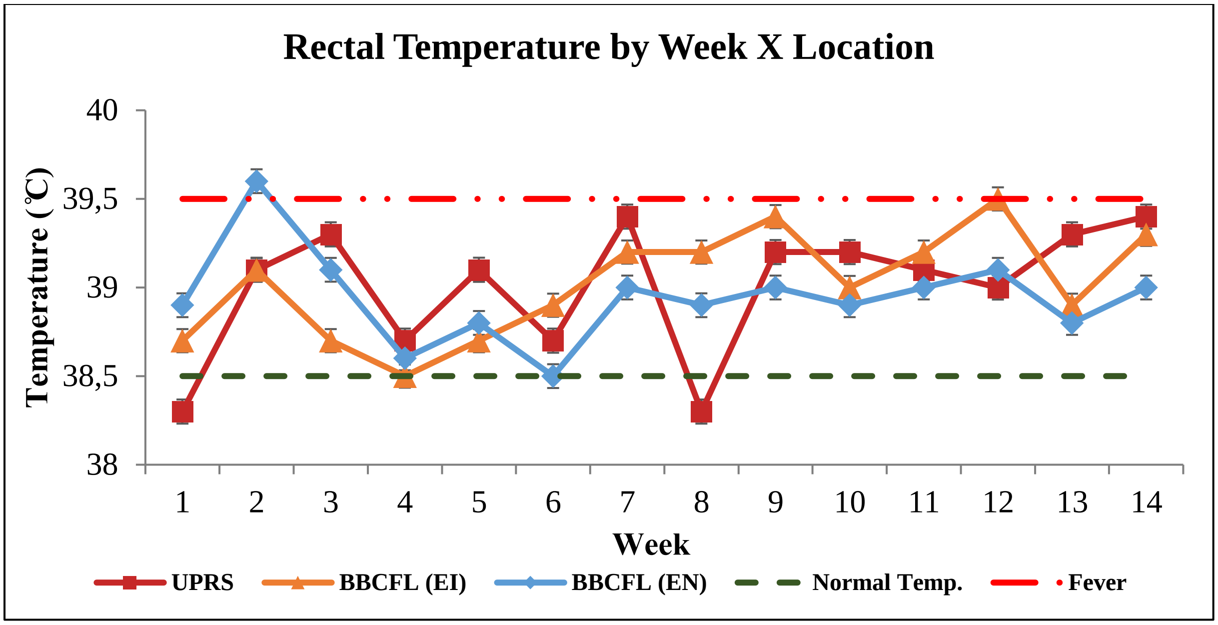

Figure 2.15: Rectal Temperature by Location over time (weeks): Rectal temperatures significantly varied between locations continually throughout the study. Model was significant by week and treatment by location (week, and trtXloc P-values: P<0.0001).

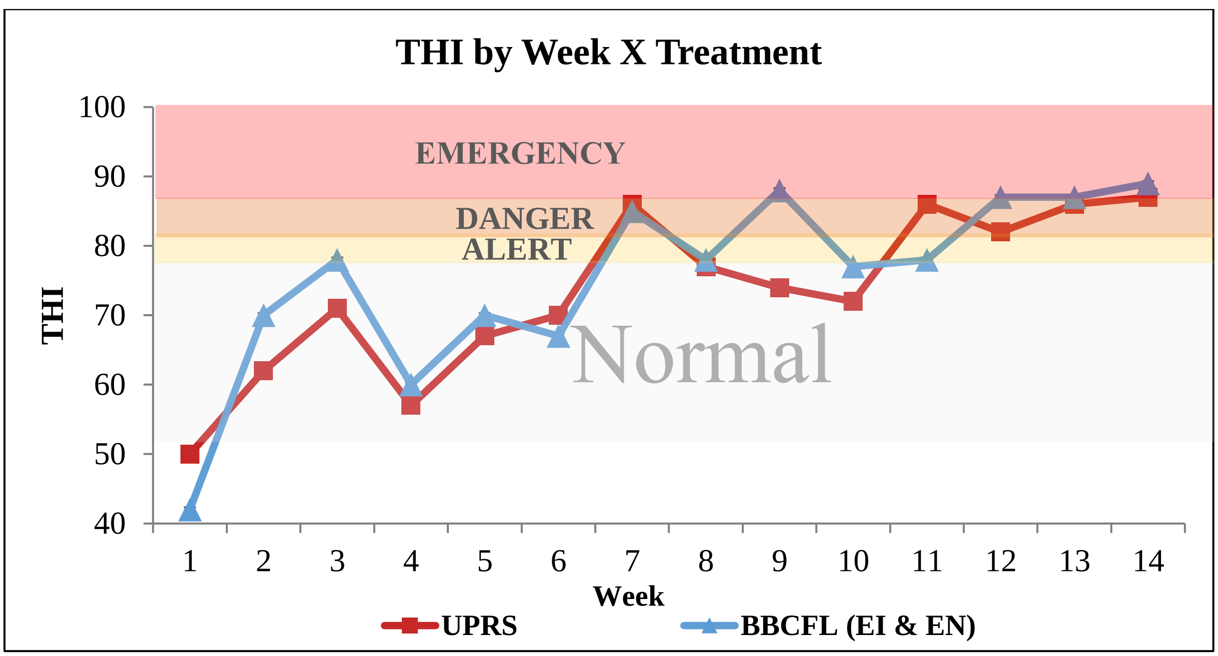

Figure 2.16: THI by Location over time (weeks): BBCFL cows were exposed to a higher THI when compared to UPRS cows. Model was significant by location, (loc(trt), P-value: P<0.0001).

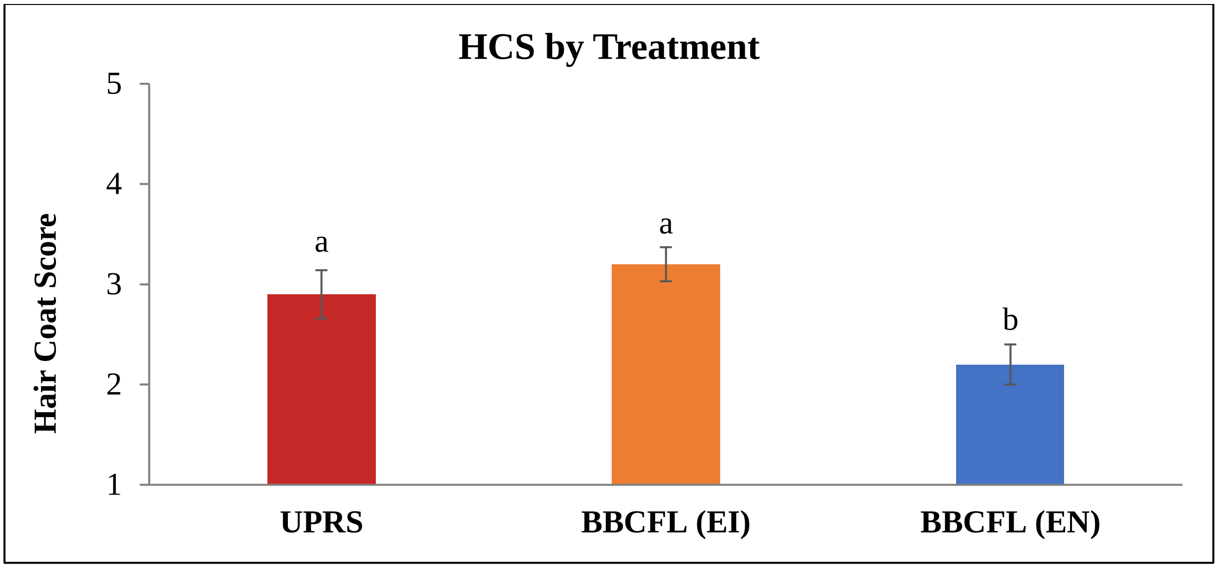

Figure 2.17: HCS by Treatment: BBCFL (EN) cows had lower scores than BBCFL (EI) and UPRS cows. No differences were observed between BBCFL (EI) and UPRS cows. Model was significant by location and treatment (loc(trt); P=0.0006; different letter superscripts indicate statistical difference).

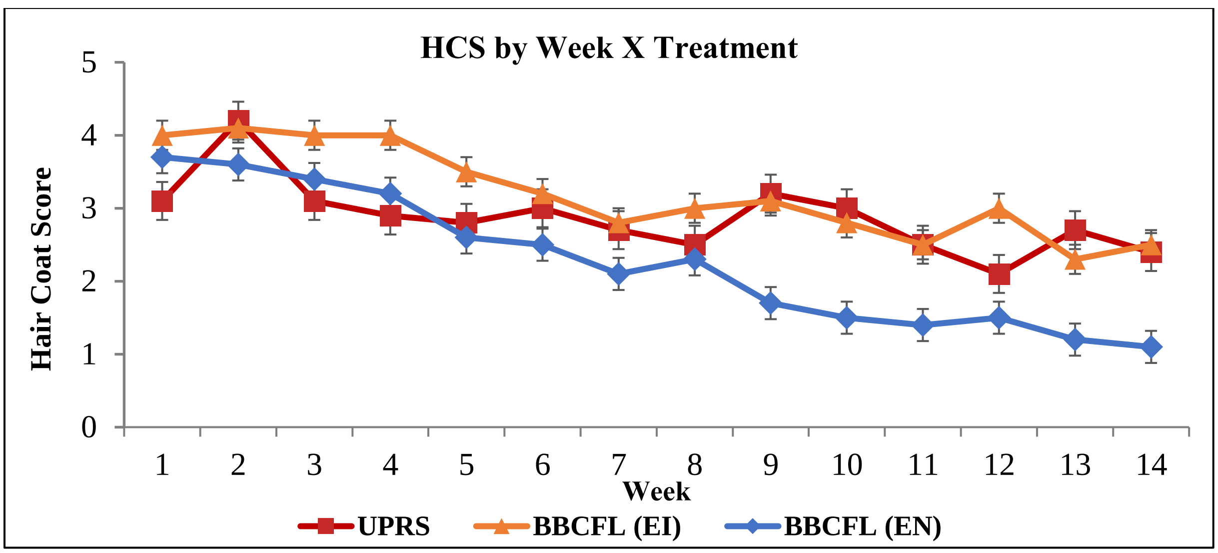

Figure 2.18: HCS by Treatment over time (weeks): BBCFL (EN) cows showed a greater capacity than BBCFL (EI) and UPRS cows to reduce the hair coat scores as the study progressed, whereas BBCFL (EI) and UPRS groups tended to show similar results. Model was significant by treatment by location over time (locXweek(trt), P<0.0001).

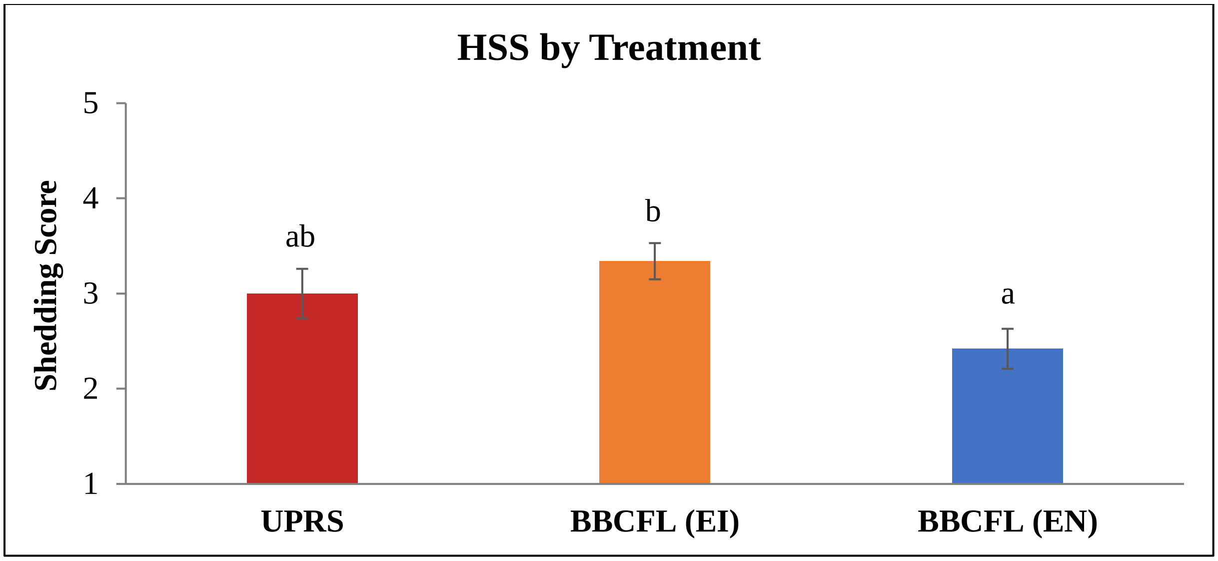

Figure 2.19: HSS by Treatment: BBCFL (EN) cows showed lower (P=0.0026) shedding scores than BBCFL (EI) cows, whilst a tendency (P=0.0636) was detected between UPRS cows and the other two groups). Model was significant by location and treatment; different letter superscripts indicate statistical difference.

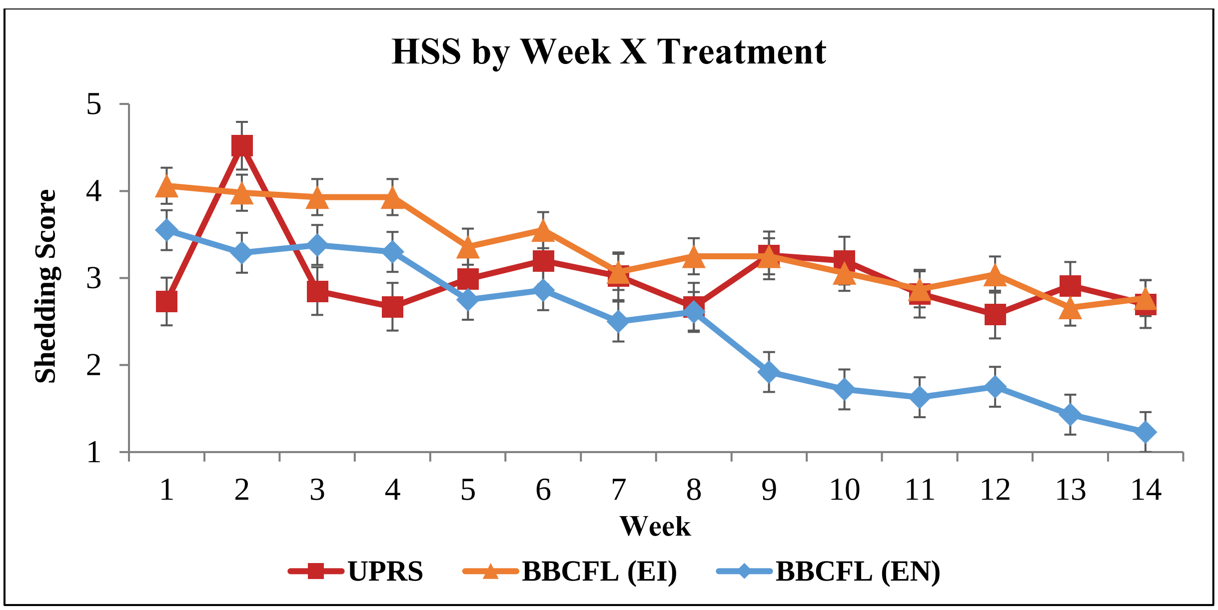

Figure 2.20: HSS by Treatment over time (weeks): BBCFL (EN) cows showed a greater capacity than BBCFL (EI) and UPRS cows to shed the hair coat as the study progressed, whereas BBCFL (EI) and UPRS groups showed similar results over time. Model was significant by week and treatment by location over time (locXweek(trt) P<0.0001).

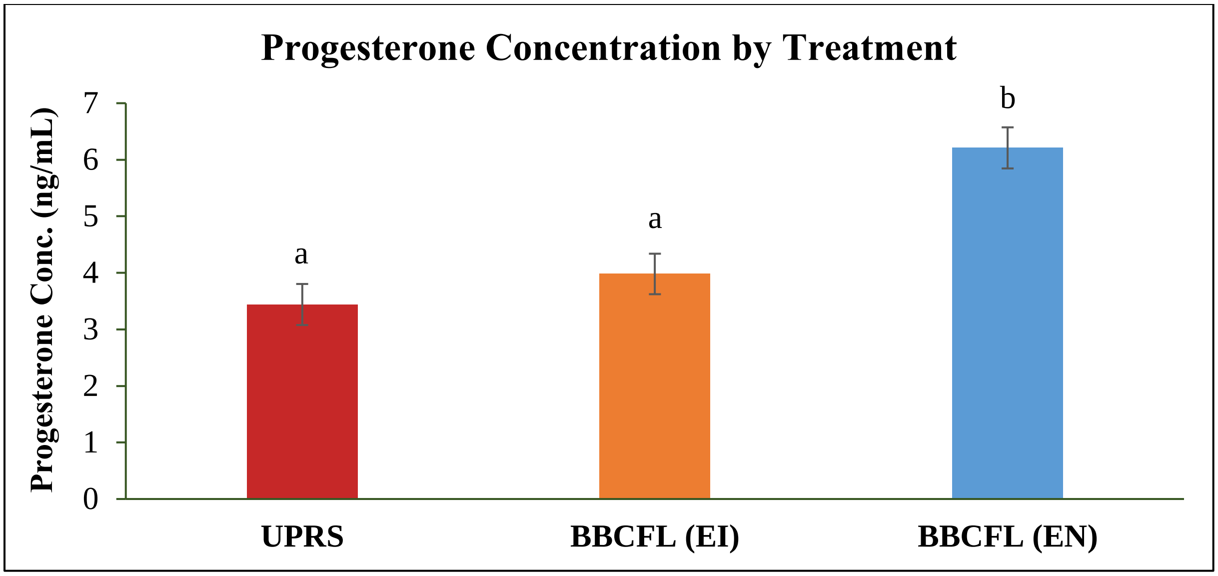

Figure 2.21: Serum Progesterone Concentration by Treatment: BBCFL (EN) cows had significantly higher progesterone concentrations (6.2 ng/mL) than BBCFL (EI) and UPRS cows (4.0 ng/mL and 3.4 ng/mL, respectively); no differences were observed between BBCFL (EI) and UPRS cows. Model was significant by location and treatment (loc(trt) P<0.0001; different letter superscripts indicate statistical difference.

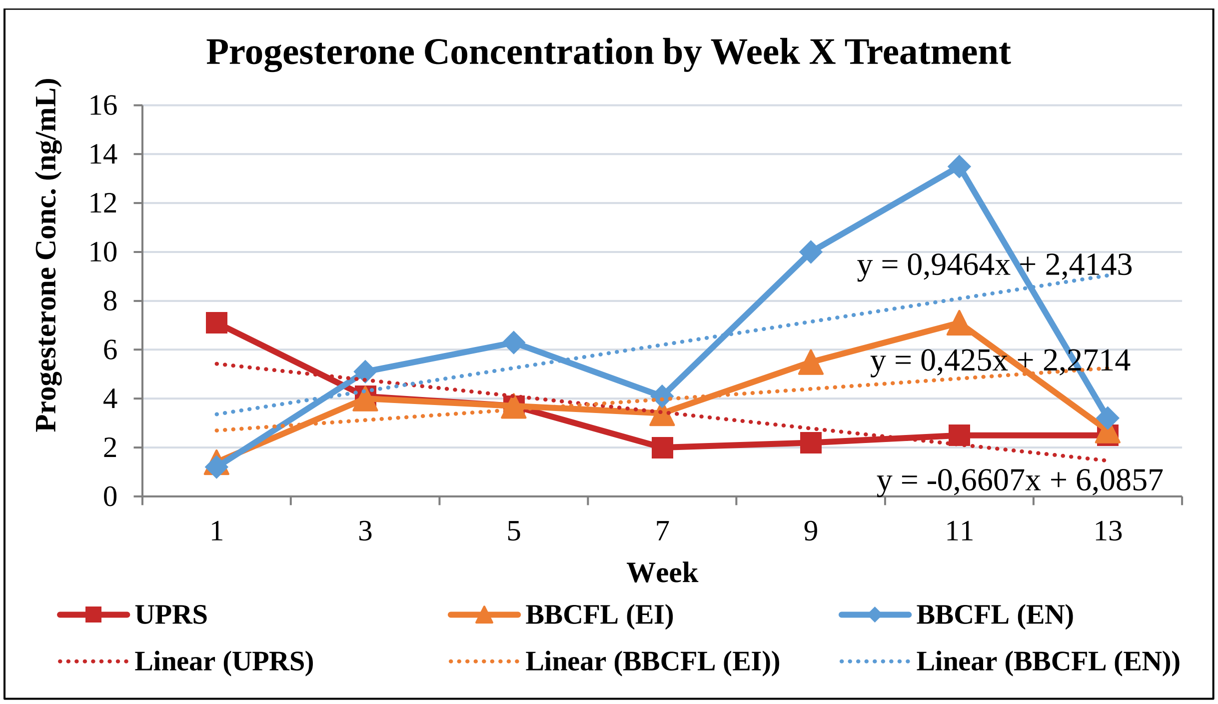

Figure 2.22: Progesterone Concentration by Treatment over time (weeks): BBCFL (EN) cows showed higher concentrations of P4 than BBCFL (EI) and UPRS cows as the study advanced, whereas BBCFL (EI) and UPRS cows reported comparable P4 concentrations throughout the study. Model was significant by location and treatment over time (locXweek(trt) P<0.0001).

CHAPTER 3

Overall Conclusions and Implications of Implementing Pulmonary Arterial Pressure as a Phenotypic Test to Identify Tolerance in Beef Cattle to Fescue Toxicosis

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OVERALL CONCLUSIONS

Since ergot alkaloids were identified as the causative agent of fescue toxicosis in cattle that grazed on endophyte-infected tall fescue pastures, multiple studies have been designed to understand the disease and develop strategies to improve the forage management and minimize its negative effects on cattle performance. Recent investigations have identified that fescue tolerance may be developed in cattle populations following long-term exposure to ergot alkaloids, and it can be determined by evaluating performance parameters within the herd and utilizing specific genetic criteria to develop phenotypic selection strategies, which can promote the heritability of these traits and genetically improve the future cattle population. With this study, a relationship between ergot alkaloid consumption and PAP is discovered, and significant differences were observed in this specific measurement, as well as in other performance parameters, between cattle groups that were exposed to endophyte-infected and novel endophyte tall fescue.

Cows that grazed on endophyte-infected fescue pastures reported significantly lower PAP mean values than the cows that grazed on novel-endophyte fescue. Contrary to the hypothesis of this study, instead of observing an increase in PAP mean values of cows that were exposed to ergovaline, the results suggest that this alkaloid compound had an inverse effect on the PAP mean values of the cows utilized in this research. Even though ergovaline was the exclusive ergot alkaloid identified in the forage samples, this ergopeptine has been previously recognized as the main causative agent of fescue toxicosis in grazing livestock. Furthermore, the magnitude of the effects on PAP mean values may also depend on the concentration of ergovaline present in tall fescue, as the differences observed in the PAP mean values are also inversely proportional to the differences in ergovaline concentrations reported by the analyses. Evaluation of the impact of specific ergovaline concentrations through extended periods of time on PAP mean values of cows would help to confirm these speculations. Further, the hematocrit results observed in this study indicate a possible interaction with ergovaline, as cows that were exposed to higher alkaloid concentrations reported higher hematocrit percentages. Considering that water is the major component of blood and increased hematocrit levels are associated to dehydration, additional research focusing on evaluating the effects of ergot alkaloids on water intake and hematological parameters of cattle could lead to more unequivocal evidence.

In addition, the performance parameters observed between animal groups in this study confirm the vast previous evidence supported by multiple studies. Cows that grazed on novel-endophyte tall fescue pastures had increased weight gains, maintained better body condition and thermoregulation, and also had a superior ability to shed their winter coats throughout the study. This group also showed higher serum progesterone concentrations, which are fundamental for the maintenance of pregnancy. Further, the results observed between the cows exposed to different ergovaline concentrations at different locations also correspond to previous evidence, as the group that consumed the highest concentration of alkaloids reported greater susceptibility to heat stress, a reduced capacity to shed their winter hair coats, and the lowest serum progesterone concentrations. These results confirm the negative impact of fescue toxicosis on cattle performance.

Overall, these results provide a new perspective to analyze the effects of fescue toxicosis on cattle physiology. However, additional studies are necessary to determine if PAP can be utilized as a phenotypic test to identify tolerance in beef cattle to this disease. These investigations should evaluate PAP variations in increased and more diverse population sizes through longer periods of time, which include significant environmental variations and different ergot alkaloid concentrations. Considering that PAP is moderately heritable, it is also necessary to determine if the results obtained from the cows utilized in this study would be similar to those reported by their offspring. Undoubtedly, future results related to this subject will provide more transparent and applicable insight to benefit the beef cattle industry.

IMPLICATIONS

The evaluation of the interaction between PAP and fescue toxicosis is innovative to beef cattle research in the United States. The results obtained in this study provide a new perspective to analyze the impact of ergot alkaloids on the cardiopulmonary system of cattle, and demonstrates that this multifaceted disease demands a multifaceted research approach. Additionally, this evidence encourages the investigation of potential implications of fescue toxicosis on parameters like feed and water efficiency, trait heritability and cattle selection methods. Further evaluations of the interactions between ergot alkaloid intake and physiological parameters like PAP, blood volume and hematocrit could provide unprecedented knowledge about the effects of the disease in the bovine organism, and generate new concepts that can be utilized to reduce the negative consequences of fescue toxicosis and improve cattle productivity in the Southeastern U.S.