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Targeting Inflammation in Heat-Stressed Wethers Improves Growth and Efficiency and Alters Body Composition; A Brief Exploration and Application of Extension Principles

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TARGETING INFLAMMATION IN HEAT-STRESSED WETHERS IMPROVES GROWTH AND EFFICIENCY AND ALTERS BODY COMPOSITION; A BRIEF EXPLORATION AND APPLICATION OF EXTENSION PRINCIPLES

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TARGETING INFLAMMATION IN HEAT-STRESSED WETHERS IMPROVES GROWTH AND EFFICIENCY AND ALTERS BODY COMPOSITION; A BRIEF EXPLORATION AND APPLICATION OF EXTENSION PRINCIPLES

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The objective of our first study was to determine how administering anti-inflammatory dexamethasone and ω-3 polyunsaturated fatty acid (**PUFA**)-rich fish oil affects growth efficiency and body composition in heat-stressed finishing lambs. Commercial wethers were randomly assigned to be fed under heat stress (35°-40°C) or thermoneutral (19°C, n = 10) conditions for 30 d, and controls were pair-fed to eliminate differential feed intake. Heat-stressed wethers were randomly assigned to receive clinical-dose dexamethasone IM injections every 72 h, twice daily fish oil capsule oral boluses, or placebos. Heat stress decreased ($P < 0.05$) growth and efficiency, but dexamethasone and fish oil supplementation recovered these performance measures. Heat stress also decreased ($P < 0.05$) predictive body composition metrics that were at least partially improved by administration of dexamethasone and fish oil. Proximate analyses of muscles showed that heat stress decreased ($P < 0.05$) percentage of protein and increased ($P < 0.05$) percentage of intramuscular fat, neither of which was improved by dexamethasone or fish oil. Immunohistochemistry revealed that heat stress decreased ($P < 0.05$) myoblast differentiation and muscle fiber size, but anti-inflammatory supplementation recovered differentiation only. Plasma IGF-1 concentrations were not different among groups throughout the study. These findings demonstrate how heat

stress-induced inflammation contributes to impaired growth, efficiency, and body composition observed in heat-stressed feeder lambs. However, targeting inflammation with dexamethasone or fish oil recovers many of these deficits.

The Cooperative Extension Service, created in 1914, facilitates interaction and communication between academics and the general public related to agriculture and public health. Agricultural extension services benefit producers of agricultural products and inform the research programs at land-grant universities. Extension methodology follows a general pattern that directs the flow of information, regardless of the discipline. This chapter describes the creative processes for written extension materials and digital media materials using a recently created NebGuide and an extension podcast as respective illustrations of the methodology in practice. Extension programming and content delivery via a broader range of modes will better ensure effective communication and assist extension professionals in reaching wider and more diverse audiences.

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Soli Deo Gloria

Dedication

To my parents and grandparents,
Sam & Jody Most, Clint & Nettie Nordhausen, and Don & Anita Most,
Who always point me to the Light.

CHAPTER 1 - LITERATURE REVIEW

Portions of this chapter were published as a review in *Animals*, which is a peer-reviewed publication.

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INTRODUCTION

Heat stress is a long-standing barrier to global livestock production due to its impact on animal health and performance (Carnovale and Phillips, 2020; Zhang et al., 2020). Indeed, the extended periods of heat stress common to much of the inhabited world increase morbidity and mortality rates, reduce growth and efficiency, and diminish the amount and quality of meat or milk produced by each animal (Hahn, 1999; St-Pierre et al., 2003). Moreover, the continued emergence of climate change makes mitigation strategies for the effects of heat stress increasingly important to the sustainability of the livestock industry (Gregory, 2010). In the US and Europe, heat waves are projected to occur with greater frequency, intensity, and duration over the next century, including in regions for which such events are historically uncommon (Meehl and Tebaldi, 2004). Greater peak daytime temperatures during these events are detrimental for livestock (Hahn and Mader, 1997), but elevated nighttime temperatures substantially worsen outcomes by reducing windows for heat dissipation (Brown-Brandl et al., 2005a). Animal

well-being experts have noted that livestock housed in confined areas such as feedlots and dairies are particularly susceptible to heat stress, as they are often restricted in their ability to engage in alleviation behaviors such as seeking shade or wading in water when these options are not provided by the infrastructure of the facility (Mader, 2014; Grandin, 2016; Lees et al., 2019). Although confinement is necessary during certain stages of food animal production, greater mortality and morbidity from heat stress in these populations is a major animal welfare issue. Greater death loss and reduced production associated with heat stress also threaten the economic sustainability of the livestock industry. For example, estimates based on 2018 beef prices indicate that each feedlot steer lost during a heat event costs the producer about $5,000 (Sullivan and Mader, 2018). Most animals survive even severe heat events, however, and heat stress-associated reductions in growth and productivity cost the industry five to ten-fold more annually than heat stress-associated death loss (Sullivan and Mader, 2018). For beef cattle, heat stress during the finishing phase reduces carcass yield and quality traits such as marbling and tenderness, resulting in billions of dollars in lost revenue each year (Kreikemeier et al., 1998; Wheeler et al., 2001; St-Pierre et al., 2003). Unfortunately, strategies to improve health and production outcomes in heat-stressed animals are limited by poor understanding of the physiological mechanisms that dictate these responses. However, recent research has indicated that chronic heat stress induces systemic inflammatory responses, which appears to be one mechanism facilitating heat stress pathologies. This review highlights the evidence for how chronic heat stress induces systemic inflammation and its potential

mediating role in poor growth and body composition outcomes, as well as how it might be a target for intervention strategies.

THE IMPACT OF HEAT STRESS ON LIVESTOCK

Heat Stress Conditions

Mammals become heat stressed when heat is produced and absorbed by their body at a greater rate than it is dissipated, resulting in hyperthermia (Lees et al., 2019). The mechanisms for body heat dissipation (i.e., conduction, convection, and evaporation) are greatly influenced by environmental conditions (Renaudeau et al., 2012), as illustrated in **Figure 1.1**. Heat moves down its gradient, and thus ambient conditions that heat the ground and other surroundings to temperatures that exceed body temperatures markedly limit the effectiveness of heat dissipation by conduction. Dissipation via convection requires adequate air movement and falls substantially during periods of little to no wind, and high relative humidity in the ambient air limits evaporative heat dissipation associated with sweating and panting (Renaudeau et al., 2012). Moreover, clear skies that lack cloud cover result in greater heat input from solar radiation (Pezzopane et al., 2019). Consequently, livestock are at greatest risk for heat stress on hot, clear days with high humidity and minimal windspeed (Sparke et al., 2001). Most agricultural regions of the world experience periods of seasonal heat waves, defined as three or more consecutive days of unusually hot daytime conditions with limited nighttime cooling (Meehl and Tebaldi, 2004). Of course, heat waves are not always dependent upon season, and heat stress can occur any time animals face thermal loads to which they are unacclimated (Brown-Brandl et al., 2005a), which can be dictated by

more than just ambient air temperatures. After studying the effects of humidity on milk production for years, Hudson Kibler popularized the use of the Temperature-Humidity Index (THI) in the mid-1960s to estimate thermal loads in dairy cows under various air temperature/humidity combinations (Kibler, 1964). The use of this index, which was based on Earl Thom's model for describing human discomfort (Thom, 1958; Thom, 1959), has been expanded to other livestock species in the decades since, and in 1970 THI values were used to create the risk categories of the Livestock Weather Safety Index (Eigenberg et al., 2007). For beef cattle in feedlots, THI values of less than 74 are classified as *Normal* and would not be expected to impose stress (Nienaber and Hahn, 2007). Conversely, THI values above 75 place feedlot cattle in the increasingly concerning stress categories of *Alert* (75 to 78), *Danger* (79 to 84), and *Emergency* (greater than 84) (Nienaber and Hahn, 2007), which would be expected to result in the responses and outcomes summarized in **Table 1.1**. Most sheep breeds are more heat tolerant than cattle and do not typically exhibit signs of stress at THI values less than 82 (Marai et al., 2007). Moderate heat stress responses would be expected from sheep at THI values of 82 to 84, more severe responses would be expected at 84 to 86, and the most extreme outcomes (including substantial increases in mortality rates) would only be expected when THI values exceed 86 (Marai et al., 2007). Although THI values provide more accurate estimates of thermal load in livestock than air temperatures alone, they do not account for the contribution of solar radiation and windspeeds (Brown-Brandl et al., 2005b; Gaughan et al., 2008). In 1981, however, dairy researchers in Florida expanded the THI algorithm to include both net radiation and air movement in addition to

temperature and humidity, resulting in the Black Globe-Humidity Index (BGHI) (Buffington et al., 1981). Named for the solar radiation-absorbing, black-painted globe placed around the thermometer, BGHI more accurately predicts heat stress indicators such as changes in rectal temperatures and respiratory rates than THI alone. However, because BGHI requires additional equipment and measurements and only differs from THI under specific conditions, THI is more commonly used for livestock.

Consequences of Heat Stress

Hyperthermia

Perhaps the greatest mediator of physiological changes in heat-stressed animals is the elevation of body temperature. In feedlot sheep, rectal temperatures were increased by 0.5° to 1.5°C within hours of initiating heat stress. Moreover, rectal, corneal, and skin temperatures remained elevated until heat stress ceased weeks later, even when substantial overnight cooling occurred (Barnes et al., 2019; Swanson et al., 2020; Barnes et al., 2021). For comparison, the magnitude of these increases were comparable to the febrile response observed when sheep were injected with bacterial endotoxin (Cadaret et al., 2019a; Cadaret et al., 2021). In cattle and sheep, extreme heat stress-induced hyperthermia can cause fatal damage to the brain and other vital organs (Busby and Loy, 1997; Sula et al., 2012). In more moderate cases, hyperthermia decreases appetite and impairs molecular mechanisms for growth and metabolic efficiency (Barnes et al., 2019; Swanson et al., 2020; Barnes et al., 2021).

Hyperventilation

Increasing respiratory rate, or panting, is an important mechanism by which heat-stressed livestock can dissipate body heat (Marai et al., 2007). In fact, greater efficiency of panting appears to be a factor in the enhanced thermotolerance of some cattle breeds (Gaughan et al., 1999). Respiratory rate is a frequently used indicator of heat stress in feedlot cattle because it is an objective measurement, is influenced in a predictable manner, and does not tend to lag behind changes in ambient conditions (Brown-Brandl et al., 2005b). Cattle generally exhibit respiratory rates of about 60 breaths/minute in the absence of stress but can more than double this rate during even moderate heat stress (Hahn and Mader, 1997). Although an effective cooling mechanism, elevated respiratory rate can have negative impacts on blood chemistry when sustained. Hyperventilation for as little as 2 hours can decrease blood CO_2, which increases blood pH and results in respiratory alkalosis (Hales and Webster, 1967; Sivakumar et al., 2010).

Endocrine changes

Predictably, heat stress increases the secretion and activity of several stress hormones. Circulating concentrations of adrenaline, noradrenaline, cortisol, prolactin, vasopressin, and cytokines have all been shown to be elevated in response to chronic heat stress (Johnson and Vanjonack, 1976; Sivakumar et al., 2010; Brown-Brandl et al., 2017; Barnes et al., 2019; Swanson et al., 2020). Moreover, tissue sensitivity to stress hormones can be increased following sustained periods of heat stress (Kubik et al., 2018; Reith et al., 2020). The increased tone of stress hormones in turn affects a broad range of metabolic hormones. Decreased circulating concentrations of the thyroid hormones thyroxine (T4) and triiodothyronine (T3) have been observed in heat-stressed cattle and

small ruminants (Magdub et al., 1982; Sivakumar et al., 2010), which is in fact believed to aid in thermal acclimatization (Horowitz, 2001). However, thyroid hormones also potentiate the anabolic outcomes of growth hormone (GH) signaling (Root et al., 1986; Capuco et al., 1999), an effect that is lost with the diminished secretion of the former. Moreover, circulating GH concentrations are reduced in heat-stressed cattle (McGuire et al., 1991), whereas concentrations of the appetite-suppressing hormone leptin are increased due to greater stimulation from cortisol (Leal-Cerro et al., 2001; Archana et al., 2018).

Anorexia and poor growth performance

Among the greatest barriers to feedlot production in chronically heat-stressed livestock is reduced feed intake (Mitlöhner et al., 2001; Gaughan and Mader, 2009). Indeed, high THI has a strong inverse correlation with dry matter intake (Chang-Fung-Martel et al., 2021), which predictably reduces the rate and efficiency of weight gain and if sustained can ultimately affect the animal's health and well-being (Grandin, 2016; Russi et al., 2019; Nicolás-López et al., 2021). A recent study of heat-stressed feedlot wethers found that they had less fat-free lean tissue relative to their total bodyweight (Gibbs et al., 2019). Moreover, loin muscles and 9^{th}-12^{th} rib cutouts from these heat-stressed wethers contained less fat (Swanson et al., 2020). Similar observations were reported in goats, as heat stress decreased loin-eye area and fat score (Archana et al., 2018). In cattle, heat stress disproportionally reduced subcutaneous fat deposition relative to other fat deposits, perhaps to diminish its insulating effect on heat dissipation (Mader and Davis, 2004).

Although the mediating role of reduced intake is well documented, results from pair-feeding studies (i.e., studies in which the amount of feed offered to thermoneutral control animals is adjusted to be equivalent to the amount consumed by heat-stressed animals) have demonstrated that heat stress reduces growth performance through other mechanisms as well. These intake-independent changes may vary with the intensity and duration of the heat stress but are typically associated with disruptions in metabolic processes (Rhoads et al., 2009; Bernabucci et al., 2010; Wheelock et al., 2010). Large scale pair-feeding studies in feedlot cattle are rare due to their high costs and logistical difficulties, but a study performed in pair-fed mice estimated that around 50% of heat stress effects were due to intake-independent factors (Xiao et al., 2020). Such mechanisms alter endocrine and metabolic aspects of growth regulation, which helps to explain poor growth performance observed in heat-stressed feedlot lambs, even when thermoneutral counterparts were pair fed (Gibbs et al., 2019; Swanson et al., 2020). One prominent example of an intake-independent mechanism would be cellular oxidative stress, as greater production of free radicals increases plasma membrane and mitochondrial damage, impairs metabolic signaling, increases protein catabolism, and decreases protein synthesis (Belhadj Slimen et al., 2016). In swine, as little as 12 hours of heat stress was enough to induce oxidative stress in muscle, leading to disruption in multiple regulatory processes (Ganesan et al., 2017). These and other intake-independent changes in tissue growth during heat stress are associated with altered gene expression. Indeed, expression for stress response mediators such as c-Fos, acute-phase proteins, RNA binding proteins, adrenergic signaling components, and protein ubiquitination was

greater in muscle and fat tissues from heat-stressed lambs and cattle (Kubik et al., 2018; Reith et al., 2020). However, not all changes in gene expression are negative. For example, muscle from chronically heat-stressed cattle and goats expressed greater mRNA for heat shock proteins (Rhoads et al., 2008; Archana et al., 2018), which are key facilitators of protein stability that protect against heat-induced protein damage (Fernández-Fernández and Valpuesta, 2018). In fact, single nucleotide polymorphisms for heat shock protein 70 identified in two African cattle breeds appear to contribute to their enhanced thermotolerance (Mkize and Zishiri, 2020).

Common abatement strategies for heat stress

Because feedlot animals are almost always housed outdoors, they are fully subject to extremes in ambient temperatures, humidity, and solar radiation conditions. For these animals, the risk of heat stress is increased not only by their limited ability to pursue natural shade or breeze but also by the greater metabolic heat load produced by their high energy diets (Blackshaw and Blackshaw, 1994). For decades, heat stress abatement strategies in confined livestock have centered on three main methods for mitigating high thermal load: 1) protection of animals via environmental modifications, 2) genetic selection for greater heat tolerance, and 3) altering nutritional management approaches to best fit the changing nutritional requirements (Beede and Collier, 1986).

Protection via environmental modification

A number of different types of physical barriers have been used to reduce thermal input by blocking radiation and to increase heat dissipation by enhancing convection and evaporation. Structures built to provide feedlot cattle with greater shade have been

associated with reduced respiration rates and core body temperatures (Mitlöhner et al., 2001; Brown-Brandl et al., 2005b; Brown-Brandl et al., 2017), which is consistent with a less severe stress response. Providing shade to feedlot cattle also increased their dry matter intake, average daily gain, and final body weight for the finishing period, and increased the percentage of animals grading as USDA Choice at harvest (Mitlöhner et al., 2002). The efficacy of shade structures are of course dependent upon their design and the materials used, which must be weighed against the cost (Armstrong, 1994; Grandin, 2016). The use of sprinklers to wet the ground in pens can provide brief reductions in radiation from the soil surface but can also increase air humidity and may create mud buildup (Mader and Griffin, 2015). Using sprinklers to wet the cattle directly can reduce thermal load in drier climates but is ineffective or even harmful in areas with high humidity, as droplet barriers in the hair coat can disrupt non-evaporative heat dissipation (Hahn, 1985; Mader et al., 2007). Moreover, cattle responses to heat stress are worsened upon discontinuation of sprinklers after prolonged use due to de-acclimation (Sullivan and Mader, 2018). Thus, sprinkler cooling is best suited for short-term use in low-humidity environments.

Genetic selection for heat tolerance

Genetic selection for traits that reduce the impact of thermal load is an effective strategy for combating heat stress, particularly in areas for which heat stress is common. Although a popular selection criterion in feedlot cattle for most of the last century has been darker coat color, these absorb substantially more solar radiation than lighter coats (Riemerschmid, 1943; Blackshaw and Blackshaw, 1994). Consequently, cattle with dark

coats had elevated body temperatures and panting rates during mild to moderate heat stress and greater mortality rates from extreme heat events compared to those with lighter coats (Busby and Loy, 1997; Mader et al., 2002). Similarly, hair sheep with brown or black coats exhibited greater rectal temperatures and respiratory rate than sheep with white coats due to their increased absorption of solar radiation (McManus et al., 2011). Thermal tolerance can also be improved by selecting animals with greater *Bos indicus* influence, as these breeds are more adapted to hot and humid environments because of their geographical origin (Hansen, 2004). Regardless of coat color, *Bos indicus* breeds have lower metabolic rates than *Bos taurus* breeds and thus produce less metabolic heat (Frisch and Vercoe, 1977; Taye et al., 2017). They also express a greater capacity for sweating and non-evaporative cooling (Finch, 1985; Gaughan et al., 1999; Hansen, 2004). As a result, cattle with complete or partial *Bos indicus* composition exhibit less severe hyperthermia, hyperventilation, anorexia, and growth restriction when experiencing heat stress (Hammond et al., 1996; Mateescu et al., 2020). Additionally, there is substantial variation in thermal tolerance among *Bos taurus* breeds. For example, Senepol and Romosinuano cattle presented less severe increases in body temperature and respiratory rates than Angus cattle during severe heat stress (Hammond et al., 1996). Additionally, Mertolenga cattle were more successful in moderating hyperthermic responses to heat stress than Alentejana, Frisian, or Limousine cattle, as they appeared to utilize a more robust combination of heat dissipation mechanisms (Pereira et al., 2014). Of course, selecting for improved tolerance to heat stress must be weighed against the potential for decreased growth efficiency, carcass yield, and quality traits associated with

some heat-tolerant breeds, and these decisions must be made in advance of heat events (Elzo et al., 2012).

Nutritional management of heat-stressed livestock

Digestion and metabolism are heat-generating processes, and thus reduced intake is actually a coping mechanism to limit the body's endogenous heat increment (Sullivan and Mader, 2018). This creates two potential objectives for feeding strategies during heat stress conditions: a) helping to reduce the animal's digestive/metabolic heat increment and b) minimizing the impact of lower intake on growth performance. The amount of heat produced by digestion/metabolism is dependent upon the diet's components. Specifically, fibrous roughages are associated with large heat increments, whereas nutrient-dense concentrate ingredients are associated with more moderate heat increments (Sullivan and Mader, 2018). Rations used by feedlots typically contain mixtures of roughages and concentrate ingredients, and thus heat increment of the total diet can be manipulated by reducing the amount of feed consumed (heat-stressed animals often do this voluntarily) or by altering the roughage/concentrate ratios of the ration (Sparke et al., 2001). Indeed, temporarily restricting dry matter intake to approximately 75% of normal *ad libitum* intake was shown to reduce body temperatures in feedlot cattle, even when diets contained a relatively high proportion of roughage (Mader et al., 2002; Mader, 2003). In addition to changing ration formulations or reducing the amounts fed, a number of different supplements offer varying degrees of protection from heat stress. In feedlot animals, nutrient supplements as diverse as electrolytes, yeast, rumen-protected carbohydrates, and free ferulic acid created improvements ranging from greater water

intake to reduced body temperatures, respiration rates, blood cortisol concentrations, and protein oxidation rates (Mader et al., 2010; Broadway et al., 2019; Russi et al., 2019; Valadez-García et al., 2021). Dietary additives such as the β agonists ractopamine and zilpaterol were also effective in moderating heat-induced hyperthermia and hyperventilation (Boyd et al., 2015; Barnes et al., 2019; Swanson et al., 2020). Despite variability in the benefits they provide to heat-stressed animals, supplements are attractive options because they do not require the financial investments of structural interventions and are not associated with the potential lost production of thermotolerant genetic selection.

THE ROLE OF INFLAMMATION IN HEAT STRESS

The impact of heat stress on the immune system is complex and dynamic. When heat stress is associated with a spike in circulating cortisol due to reduced nutrient intake, the immune system as a whole can be suppressed (Bagath et al., 2019). However, recent studies show that heat stress often results in little or no increase in circulating cortisol, particularly when there is only modest reductions in dietary intake (Brown-Brandl et al., 2017; Hall et al., 2018; Swanson et al., 2020). Consequently, heat stress frequently increases inflammatory components of the immune system (Abdelnour et al., 2019), as summarized in **Figure 1.2**. Studies have reported changes in circulating leukocyte populations in heat-stressed feedlot animals, as commercial finishing heifers without access to shade during mild to moderate heat stress exhibited greater neutrophil and lymphocyte concentrations as well as neutrophil:lymphocyte ratios than those with shade (Mitlöhner et al., 2002; Brown-Brandl et al., 2017). Feedlot lambs that were exposed to

substantial daytime heat stress for 3 to 4 weeks exhibited greater circulating concentrations of total leukocytes, lymphocytes, monocytes, and granulocytes regardless of whether controls were or were not pair fed (Barnes et al., 2019; Swanson et al., 2020). Inflammatory cytokines are produced by these leukocytes (Carswell et al., 1975; Borish and Steinke, 2003; Zelová and Hošek, 2013), and consequently these feedlot lambs also exhibited greater circulating concentrations of TNFα by the 2nd week of heat stress (Swanson et al., 2020). In dairy cattle, heat stress increased circulating concentrations of leukocyte-derived TNFα, IL-6, IL1β, and INFγ even in the presence of modest increases in circulating cortisol concentrations (Min et al., 2016; Chen et al., 2018; Park et al., 2021). Oxidative cellular stress is a major stimulant of cytokine secretion (Dodd et al., 2010), and thus the increased production of reactive oxygen species during heat stress may play a large role in the greater inflammatory tone observed in chronically heat-stressed livestock (Belhadj Slimen et al., 2016; Chauhan et al., 2021).

Inflammatory regulation of muscle growth

Postnatal skeletal muscle growth occurs by muscle fiber hypertrophy, which is facilitated by quiescent progenitors called satellite cells that are stored in the basal lamina of fibers during prenatal development (Maltzahn et al., 2014; Chal and Pourquié, 2017). In response to growth promoters, satellite cells are activated into myoblasts, which proliferate through several cycles of replication and then undergo terminal differentiation before fusing with existing muscle fibers (Bi and Kuang, 2012). This accumulation of additional myonuclei increases the DNA content of the muscle fiber and, in turn, its capacity for protein synthesis (Dhawan and Rando, 2005; Davis and Fiorotto, 2009; Ten

Broek et al., 2010). Myoblast function, protein synthesis, and muscle growth are influenced substantially by cytokines and other inflammatory factors, as illustrated in **Figure 1.3**. When myoblasts isolated from fetal sheep were incubated with TNFα or IL-6, they exhibited reductions in proliferation and differentiation rates (Posont et al., 2018). Similar effects of these cytokines were observed on differentiation rates in myoblast cell lines (Al-Shanti et al., 2008). TNFα also suppressed protein synthesis in human primary myoblasts co-incubated with IGF-1 (Frost et al., 1997). Because myoblasts play a rate-limiting role in muscle growth, their functional impairment by cytokines causes a predictable reduction in muscle mass. Early studies showed that exogenous administration of TNFα or IL-1α to rats induced weight loss and diminished their whole-body protein content (Tracey et al., 1988; Fong et al., 1989). Elevated concentrations of TNFα and IL-6 in circulation promote repartitioning of amino acids away from protein synthesis in skeletal muscle (Colditz, 2002). In fact, heightened systemic inflammation is believed to be the primary cause for reduced performance in feedlot cattle with respiratory infections, as these animals exhibit decreased average daily gain, carcass weight, fat thickness, and marbling (Schneider et al., 2009; Gifford et al., 2012). Even prenatal exposure to inflammatory cytokines can restrict muscle growth, as maternofetal inflammation in rats decreased fetal mass, hindlimb cross-sectional area, and muscle fiber size (Cadaret et al., 2019b). The effects of inflammation on myoblast function and protein synthesis in muscle coincide with disrupted insulin signaling. Indeed, primary rat soleus muscle incubated with TNFα or IL-6 exhibited substantially reduced rates of insulin-stimulated Akt phosphorylation (Cadaret et al., 2017).

Methods for targeting inflammation during heat stress

Systemic inflammation presents a potentially valuable target for therapeutic strategies to improve well-being and growth outcomes in heat-stressed livestock. Moreover, feedlot animals are fed mixed rations daily, which provides an opportunistic avenue to administer oral supplements that target this heightened inflammation. In this section, we discuss several anti-inflammatory products that may have potential as dietary interventions for heat stress. These are also summarized in **Table 1.2**.

Brown seaweed & seaweed extract

Brown seaweed species such as *Sargassum latifolium* and *Ascophyllum nodosum* are used frequently as supplements due to their potent antioxidant and anti-inflammatory properties (Yende et al., 2014). Indeed, brown seaweed extract was found to be effective in reducing oxidative stress and inflammation associated with residual fescue toxicity in feedlot cattle, which helped to recover carcass merit in these animals (Allen et al., 2001; Saker et al., 2001; Braden et al., 2007). When included at up to 4% of the ration for feedlot sheep, dried whole brown seaweed moderated heat stress-induced increases in circulating leukocytes, TNFα, and IL-6 in a dose-dependent manner (Ellamie et al., 2020). This in turn reduced hyperthermia and hyperventilation and recovered growth in these heat-stressed sheep. Similar effects on body temperature were observed in heat-stressed Boer goats supplemented daily with brown seaweed extract (Yates et al., 2010).

Resveratrol

Resveratrol is a bioactive extract found in grapes and other vegetation that has documented antioxidant and anti-inflammatory properties (Malaguarnera, 2019).

Although information regarding its effects in heat-stressed ruminants is limited, it has been studied in rodents and poultry. When orally supplemented to Sprague-Dawley rats during an intense 3-day heat stress period, resveratrol suppressed the rise in hepatic TNFα production and in gene expression for other cytokines and inflammatory factors (Cheng et al., 2019). Although this study did not assess systemic inflammation or growth, it is reasonable to speculate that improvements in these outcomes were possible for resveratrol-supplemented heat-stressed rats. Oral resveratrol supplementation also reduced tissue inflammation in heat-stressed chickens (He et al., 2019). Of course, the differences in digestive physiology of ruminants compared to non-ruminants and poultry may affect the bioavailability of orally supplemented resveratrol, and thus investigation in ruminant livestock proper is warranted.

Turmeric curcumin

Curcumin is the bioactive compound found in the extract of roots from the *Curcuma longa* plant (commonly known as turmeric) (Menon and Sudheer, 2007). It has a historical presence in Eastern medicine, and its antioxidant and anti-inflammatory properties have been demonstrated in sheep (Jiang et al., 2019), among other animals. Like many supplements, studies using curcumin as an intervention for heat stress have not been performed in ruminant livestock to our knowledge. However, heat-stressed rats had less severe increases in renal TNFα, IL-6, and IL-1β expression when receiving oral supplementation of curcumin (Zhao et al., 2021). This was perhaps indicative of reduced inflammation in a broader range of tissues, as it also coincided with less muscle damage. Despite its well-documented anti-inflammatory properties, curcumin exhibits notably

poor gastrointestinal absorption when administered orally (Hoehle et al., 2006). Although strategies to improve bioavailability by identifying protective molecular structures and curcumin metabolism inhibitors are ongoing (Liu et al., 2016), it should be noted that this is currently a major limitation of oral curcumin supplementation.

Vitamin E + Se

The antioxidant activities of vitamin E and selenium (Se) when supplemented together and at supranutritional quantities have been well-characterized (Diplock and Lucy, 1973; Traber and Atkinson, 2007). Additionally, administering oral vitamin E + Se to ewes prevented heat stress-induced increases in skeletal muscle gene expression for TNFα and NF-κB, which is consistent with reduced inflammation (Chauhan et al., 2014a). This in turn resulted in less severe hyperthermia, hyperventilation, and tachycardia under heat-stress conditions (Chauhan et al., 2014a; Chauhan et al., 2014b). A similar study in goats also found that vitamin E + Se supplementation suppressed the heat stress-induced rise in body temperatures and respiratory rates (Sivakumar et al., 2010). These goats had less severe increases in circulating cortisol and prolactin and less severe reductions in circulating thyroid hormones. Although the free radical-scavenging activity of vitamin E + Se clearly improves the inflammatory status of heat-stressed livestock, it is worth noting that the high cost of these supplements can be limiting (Bellés et al., 2019).

Omega-3 Polyunsaturated Fatty Acids

The capacity for omega-3 polyunsaturated fatty acids (ω-3 PUFA; e.g., eicosapentaenoic acid, EPA; docosahexaenoic acid, DHA) to mitigate inflammatory

cytokine production and signaling has been documented in animals and cell lines (Caughey et al., 1996; Liu et al., 2013; Velten et al., 2014; Chen et al., 2017; He et al., 2017; Inoue et al., 2017; Zhu et al., 2018; Qiu et al., 2019). Additionally, ω-3 PUFA can also increase production of some anti-inflammatory cytokines (Gu et al., 2016; Soto et al., 2020). Studies in cattle and sheep have shown that dietary supplementation of ω-3 PUFA can improve growth performance even in animals that are under little or no acute stress (Carranza Martin et al., 2018; Nickles et al., 2019; Mohtashami et al., 2021; Roque-Jiménez et al., 2021). Thus, it is not surprising that daily supplementation of ω-3 PUFA-rich fish oil to heat-stressed feedlot lambs mitigated the rise in circulating granulocytes, granulocyte:lymphocyte ratios, body temperatures, and respiratory rates, which in turn improved muscle growth and rescued intramuscular fat content (Grijalva et al., 2021; Most et al., 2021). In heat-stressed dairy calves, fish oil reduced circulating TNFα and other inflammatory indicators, which was associated with reduced body temperatures and respiratory rates as well as improved feed efficiency (Mohtashami et al., 2021). Although fish oil is an effective and relatively inexpensive option for targeting inflammation, it should be noted that its taste and smell can create an aversion for some animals and can even result in reduced feed intake (Wistuba et al., 2006).

Probiotics

There is substantial evidence for protective effects of probiotics from yeast and other sources in heat-stressed poultry, but evidence in mammalian livestock species is less robust. However, a recent study in rats found that oral supplementation of probiotics from *L. acidophilus* and *S. cerevisiae* with and without selenium enrichment during a 42-

day heat stress period moderated indicators of hepatic inflammation and oxidative stress (Malyar et al., 2021). Specifically, increased gene expression of mRNA encoding TNFα, IL-6, COX-2, NFκB, HSP70, and HSP90 was less severe in liver tissues from heat-stressed rats receiving the once-daily supplements. Additionally, heat stress-induced reductions in gene expression for the antioxidants GPX1, SOD1, and Nrf2 were less severe in probiotic-supplemented rats. A recent study in feedlot heifers found that dietary supplementation of yeast-based probiotics for 50 days prior to a 7-day heat-stress challenge reduced the rise in body temperature and respiration rates (Broadway et al., 2019). However, these were not concurrent with any changes in circulating leukocyte populations and may have been largely the result of increased water intake by supplemented heifers during the heat-stress period. In pigs that were heat stressed for 28 days, addition of live yeast to the diet modestly reduced circulating concentrations of TNFα compared to unsupplemented heat-stressed pigs (Mayorga et al., 2021). However, TNFα concentrations of the heat-stressed pigs were comparable to respectively supplemented, pair-fed thermoneutral controls. Moreover, yeast supplementation did not appear to improve heat stress-induced changes in body temperatures, respiratory rates, metabolic indicators, or growth efficiency.

CONCLUSIONS

Chronic heat stress induces systemic inflammation, characterized in part by greater circulating leukocyte and cytokine concentrations, which contributes to hyperthermia, hyperventilation, reduced growth performance, and compromised well-being. This greater inflammatory tone is particularly disruptive of muscle growth, as cytokines

diminish the capacity of myoblasts to properly facilitate muscle fiber hypertrophy. In addition, inflammation reduces metabolic efficiency, as more nutrients are repartitioned for homeostatic mechanisms. Livestock maintained in confinement systems are at increased risk for heat stress due to their limited ability to self-protect by seeking shade or other cooler areas. However, well-being and productivity may be improved in these animals by dietary supplementation strategies that target the chronic inflammation associated with heat stress. Importantly, therapeutic reduction of systemic inflammation provides an opportunity to reduce the impact of heat stress in feedlot animals without manipulating their natural reduction in dietary intake, which is itself a heat stress-abating behavior. Moreover, limiting systemic inflammation and its impact on muscle growth processes in heat-stressed animals may also benefit their resumption of growth following the heat event. Heat stress is a major barrier to sustainable livestock production, and thus continuing the pursuit of nutraceutical strategies to improve health and productivity outcomes in heat-stressed food animals by targeting inflammation is warranted. Therefore, the objective of the study in Chapter II was to evaluate the whole-body & muscle growth and body composition of heat-stressed wethers supplemented with the anti-inflammatory agents dexamethasone or ω-3 PUFA-rich fish oil pills. To our knowledge, no studies of this kind are described in the literature and the relationships between heat stress, inflammation, and muscle growth dynamics are not well understood. Thus, we sought to characterize the effects of supplementation on growth and body composition outcomes with the goal of identifying a nutraceutical target for use in the ruminant feedlot livestock context.

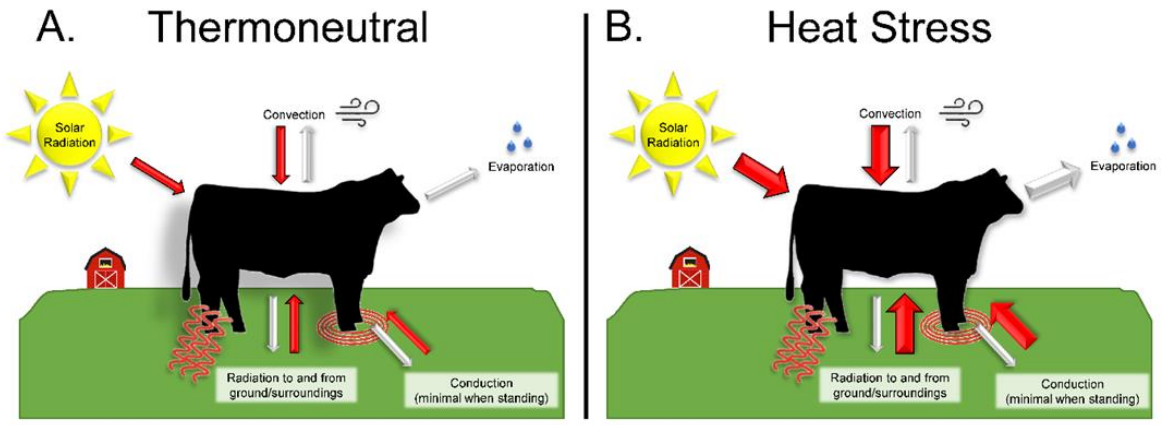

Figure 1.1 Thermal energy is exchanged between the animal and environment by three main processes: convection, conduction, and radiation.

In livestock, conduction is generally limited to recumbent positions. Evaporation of sweat and moisture from the respiratory tract is an important mechanism for heat dissipation. Under thermoneutral conditions (A.), thermal input from the environment is roughly equal to dissipation, and the animal does not expend additional energy to maintain homeostatic body temperature. During heat stress (B.), thermal input exceeds normal dissipation, and the animal must engage additional processes for heat dissipation to maintain a stable body temperature. When heat stress is extreme, this homeostasis may be lost, resulting in hyperthermia.

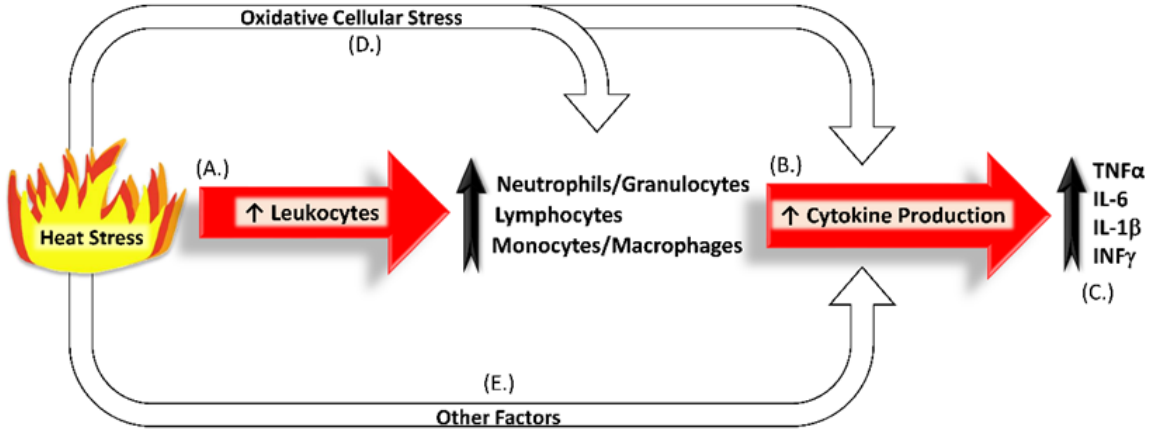

Figure 1.2 Heat stress increases components of systemic inflammation.

This includes circulating populations of total leukocytes, granulocytes, lymphocytes, and monocytes (A.) (Mitlohner et al., 2002; Brown-Brandl et al., 2017; Barnes et al., 2019; Swanson et al., 2020). Along with other tissues, these circulating leukocytes produce inflammatory cytokines in greater amounts (B.) (Carswell et al., 1975; Borish and Steinke, 2003; Zelova and Hosek, 2013), resulting in greater cytokine concentrations in the bloodstream (C.) that contribute to the enhanced inflammatory tone observed in heat-stressed livestock (Min et al., 2016; Chen et al., 2018; Swanson et al., 2020; Park et al., 2021). At the same time, oxidative cellular stress (D.) and other factors not discussed in this review (E.) can further stimulate cytokine synthesis and release (Dodd et al., 2010; Belhadj Slimen et al., 2016; Chauhan et al., 2021).

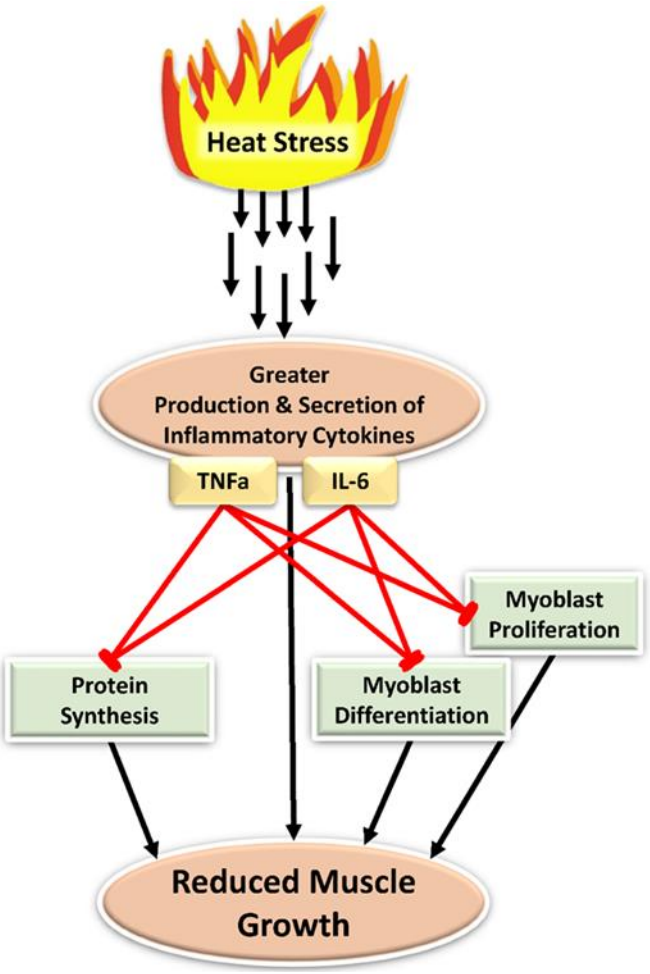

Figure 1.3 Heat stress-induced inflammatory factors interfere with the major processes that facilitate muscle growth.

Specifically, heat stress increases circulating leukocyte populations (Mitlohner et al., 2002; Brown-Brandl et al., 2017; Barnes et al., 2019; Swanson et al., 2020), which in turn contribute to greater circulating inflammatory cytokines, including TNFα and IL-6 among others (Carswell et al., 1975; Borish and Steinke, 2003; Zelova and Hosek, 2013). Exposure of myoblasts (i.e., muscle stem cells) to TNFα or IL-6 can reduce their proliferation and differentiation rates, which is detrimental to muscle growth (Al-Shanti et al., 2008; Posont et al., 2018). Additionally, exposure of skeletal muscle itself to TNFα or IL-6 reduces its protein synthesis (Tracey et al., 1988; Fong et al., 1989; Frost et al., 1997) in part by re-appropriating amino acid utilization (Colditz, 2002).

Table 1.1 Temperature-Humidity Index (THI) ranges and associated responses in livestock.

THI Category	THI Ranges by Species		Respiration	Body Temperature Divergence (°C)	Behavioral Responses	Stress Level
	Cattle[1]	Sheep[2] & Goats[3]				
Normal	< 74.0	< 82.0	Normal	0.00°	Normal	None
Alert	74.0 to 79.0	82.0 to 84.0	Steady but increased breathing	+ 0.11°	Increased standing	Mild
Danger	79.1 to 84.0	84.1 to 86.0	Rapid, shallow breaths	+ 0.28°	Bunching, ↓ feed intake	Moderate
Emergency	> 84.0	> 86.0	Deep, abdominal breaths with tongue extended	+ 0.56°	Lingering at water source	Severe

[1](Brown-Brandl et al., 2005; Eigenberg et al., 2007; Mader et al., 2010).
[2] (Marai et al., 2007; Renaudeau et al., 2012).
[3] (Renaudeau et al., 2012; Archana et al., 2018).

Table 1.2 Potential anti-inflammatory/antioxidant nutraceutical and dietary supplements for the treatment of heat stress in livestock.

Supplement	Source	Species tested	References
Brown seaweed/extract	*Sargassum* & *Ascophyllum* spp.	Cattle, sheep, goats	114 115 116 117 118 119
Resveratrol	*Vitis* spp.	Rats, chickens	120 121 122
Turmeric curcumin	*Curcuma longa*	Sheep, rats	123 124 125 126 127
Vitamin E + Selenium	Commercial supplements	Sheep, goats,	128 129 130 131 132
ω-3 PUFA[1]	EPA[2], DHA[3], fish oil	Cattle, sheep, mice, pigs, rats	133 134 135 136 137 138 139 140 141 142 143 144 145 146 147 148 149

[1]Polyunsaturated fatty acid.
[2]Eicosapentaenoic acid.
[3]Docosahexaenoic acid.

CHAPTER 2 - TARGETING INFLAMMATION IN HEAT-STRESSED WETHERS IMPROVES GROWTH AND EFFICIENCY AND ALTERS BODY COMPOSITION

Some of the findings presented in this chapter were published in the 2021 proceedings of the American Society of Animal Science, Western Section, which is peer-reviewed.

Most, M.S., P. C. Grijalva, H. N. Beer, R. L. Gibbs, Z. H. Hicks, T. A. Lacey, T. B. Schmidt, J. L. Petersen, and D. T. Yates. 2021. Dexamethasone and fish oil improve average daily gain but not muscle mass or protein content in feedlot wethers after chronic heat stress. *Transl. Anim. Sci.* 5(Suppl 1) doi: 10.1093/tas/txab163

ABSTRACT

Chronic heat stress impairs growth and productivity of feedlot livestock by reducing daily feed intake but also by mechanisms unrelated to nutrition. We recently observed evidence that systemic inflammation is one such mechanism. The objective of this study was to determine how administering anti-inflammatory dexamethasone and ω-3 polyunsaturated fatty acid (**PUFA**)-rich fish oil affects growth efficiency and body composition in heat-stressed finishing lambs. Commercial wethers were randomly assigned to be fed under heat stress (35°-40°C) or thermoneutral (19°C, n = 10) conditions for 30 d, and controls were pair-fed to eliminate differential feed intake. Heat-stressed wethers were randomly assigned to receive clinical-dose dexamethasone IM injections every 72 h (n = 8), twice daily fish oil capsule oral boluses (n = 8), or placebos (n = 9). Growth, feed intake, and body composition metrics were recorded throughout the study period. Lambs were euthanized on d 31 to measure individual muscle masses and

to collect tissue samples and 9^{th}-12^{th} rib cutouts. Heat stress decreased ($P < 0.05$) final body weight, average daily gain, and feed efficiency (i.e., gain:feed), but dexamethasone and fish oil supplementation recovered these performance measures. Heat stress decreased ($P < 0.05$) ultrasonic estimates of loin eye area, loin depth, and subcutaneous backfat thickness, bioelectrical impedance analysis (**BIA**)-estimated whole-body lean tissue mass, and actual muscle percentage of 4-rib cutouts. Administration of dexamethasone recovered ($P < 0.05$) loin eye area, loin depth, backfat thickness, and BIA-estimated lean tissue mass, but not muscle percentage of 4-rib cutouts. Supplementation with fish oil partially recovered ($P < 0.05$) ultrasound estimates and fully recovered ($P < 0.05$) BIA-estimated lean tissue mass and muscle percentage of 4-rib cutouts. Proximate analyses of several muscles showed that heat stress decreased ($P < 0.05$) percentage of protein and increased ($P < 0.05$) percentage of intramuscular fat, neither of which was improved by dexamethasone or fish oil. Immunohistochemistry of the *semitendinosus* revealed that heat stress decreased ($P < 0.05$) myoblast (i.e., muscle stem cell) differentiation and muscle fiber size. Dexamethasone and fish oil tended to recover ($P < 0.10$) deficits in myoblast differentiation but not in muscle fiber size. Plasma IGF-1 concentrations were not different among groups throughout the study. These findings demonstrate how heat stress-induced inflammation contributes to impaired growth, efficiency, and body composition observed in heat-stressed feeder lambs. However, targeting inflammation with dexamethasone or fish oil recovers many of these deficits.

INTRODUCTION

Livestock animals raised for meat production exhibit decreased growth and efficiency during heat stress (Most and Yates, 2021). Financial losses for the animal agricultural industry due to heat stress average $2.4 billion annually, with $369 million in losses for the beef industry alone (St-Pierre et al., 2003). Feedlot animals are at particular risk due to their outdoor confinement (Mader, 2003). Previous studies by our lab have shown that deficits in growth and body composition occur concomitantly with enhanced inflammatory status in heat-stressed lambs (Barnes et al., 2021). These deficits occur even when the effect of heat stress on nutrient intake is eliminated by pair-feeding of thermoneutral counterparts (Swanson et al., 2020) and could be associated with changes in insulin-like growth factor 1 (**IGF-1**), which promotes tissue growth by anabolic protein, lipid, and carbohydrate metabolism (Butler and Roith, 2001). Inflammatory cytokines including TNFα and IL-6 help facilitate muscle growth under normal conditions but impair myoblast (i.e., muscle stem cell) function and inhibit growth when sustained at high concentrations (Posont et al., 2018) such as during heat stress. In addition to the effects on growth, systemic inflammation has been associated with disruption of glucose metabolism by skeletal muscle (Barnes et al., 2019; Cadaret et al., 2019a; Swanson et al., 2020). This is a major barrier for feedlot livestock, as these metabolic deficits reduce feed efficiency, thus prolonging feeding periods and increasing the cost per unit of gain. A better understanding of the underlying inflammatory mechanisms that perturb growth efficiency and body composition during heat stress is a

fundamental step in the development of targeted therapies to improve animal well-being and productivity.

Based on our previous findings (Barnes et al., 2019; Swanson et al., 2020), we postulate that supplementing anti-inflammatory pharmaceuticals/nutraceuticals will resolve heightened inflammation and rescue growth efficiency and body composition of heat-stressed feedlot lambs. The injectable synthetic cortisol analog dexamethasone (**DEX**) was selected for its well-characterized anti-inflammatory properties and commercial availability (Rhen and Cidlowski, 2005). To explore the efficacy of an oral anti-inflammatant, we selected commercial fish oil capsules that supply high concentrations of the ω-3 polyunsaturated fatty acids eicosapentaenoic acid (**EPA**) and docosahexaenoic acid (**DHA**). Bioactive metabolites of EPA and DHA suppress inflammation by decreasing tissue infiltration of immune cells and by interrupting inflammatory signaling pathways (Bennett and Gilroy, 2016). Although polyunsaturated fatty acids can be biohydrogenated by microbes in the rumen, reports in the literature indicate that EPA and DHA are more resistant to biohydrogenation than other polyunsaturated fatty acids (Chikunya et al., 2004; Maia et al., 2007). This, combined with the relatively large dosage and twice-daily administration was expected to improve the bioavailability of the fish oil's active components.

Ultrasonography and bioelectrical impedance analysis (**BIA**) technologies can be used to estimate changes in muscle mass and body composition in live animals, which may help identify the effects of heat stress on carcass traits before harvest. Ultrasonic imagery of loin eye area (i.e., ribeye area) and subcutaneous backfat thickness has been

utilized in beef cattle (Davis et al., 1964), lambs (Moody et al., 1965), and swine (McLaren et al., 1989), and estimates can closely correlate to actual measurements. BIA uses a process of electric impulses to measure tissue reactance, resistance, and phase angles, which can be used in algorithms to predict fat-free lean mass and estimate muscle masses (Berg and Marchello, 1994; Slanger et al., 1994). In addition, immunohistochemistry can be performed in fixed muscle to identify changes in myoblast populations. Staining for paired box transcription factor 7 (**pax7**) is used to identify all present myoblasts (Maltzahn et al., 2014), and co-staining for pax7 and proliferating cell nuclear antigen (**PCNA**) is used to identify proliferating myoblasts (Kami and Senba, 2002). Staining for the transcription factor myogenin is used to identify myoblasts that have exited the cell cycle and undergone terminal differentiation, and staining for the structural intermediate-filament protein desmin is used to identify and measure myofibers (Capetanaki et al., 1997). The objective of this study was to evaluate the direct impact of chronic heat stress on growth efficiency and body composition of feedlot lambs as well as the restorative effects of intervening with the anti-inflammatory products, dexamethasone and fish oil. Feeder lambs were used as a model for feedlot cattle, as the systems that regulate growth and metabolism are comparable between the two species and the physiological differences that exist are well characterized (Sewell et al., 2009; Lundy et al., 2015).

MATERIALS & METHODS

Animals and Experimental Design.

This study was approved by the Institutional Animal Care and Use Committee for the University of Nebraska – Lincoln (**UNL**). Studies were performed at the UNL Animal Science Complex, which is accredited by AAALAC International. Crossbred Polypay wether feeder lambs (40.1 ± 0.9 kg) purchased from a single commercial source were acclimated to dietary rations and indoor conditions for a minimum of 7 d. Lambs were then individually penned and assigned via simple randomization to be housed under heat stress (40 ± 1 ℃, 35% ± 5% relative humidity) or thermoneutral (pair-fed controls; 19 ± 0.25 ℃, 15% ± 5% relative humidity; n = 10) conditions and fed a concentrate finishing diet (Lamb Grower-Finisher Comp B30 Medicated, Purina Animal Nutrition, Arden Hills, MN, USA) with free-choice access to water and a salt block for 30 d. Heat-stressed lambs were randomly assigned to 1 of 3 intervention groups. The 1st group received no intervention (i.e., heat stress; n = 8). The 2nd group received twice-daily oral omega-3 fish oil soft gels bolus (i.e., heat stress+fish oil; 1,200 mg; Nature Made Nutritional Products, West Hills, CA, USA; n = 8) containing 360 mg eicosapentaenoic acid (**EPA**) and 240 mg docosahexaenoic acid (**DHA**) at 0800 and 1600. Placebos for all other groups were empty gelatin capsules (size # 000, Torpac Inc., Fairfield, NJ, USA). The 3rd group of heat-stressed lambs were administered 0.15 mg/kg IM dexamethasone (i.e., heat stress+DEX; MWI Animal Health, Boise, ID, USA; n = 8) every 72 h. Placebos for all other groups were 1-ml IM injections of physiological saline (MWI Animal Health). Thermoneutral controls were pair-fed to the average daily intake of heat-stressed groups.

Ultrasonic measurements of the loin area and bioelectrical-impedance analysis (**BIA**) estimates of body composition were recorded weekly. Fasted bodyweights were recorded on d 0 (initial) and 30 (final) to calculate average daily gain (**ADG**). Feed refusals were weighed daily at 0800 to calculate daily feed intake, which was then used to determine gain-to-feed ratio (**G:F**). On d 31, lambs were euthanized by barbiturate overdose followed by exsanguination. The gastrointestinal tract from the esophagus to rectum was removed and weighed to estimate empty bodyweight. *Biceps femoris* (**BF**), *flexor digitorum superficialis* (**FDS**), *gastrocnemius* (**GAST**), *semitendinosus* (**ST**), *soleus* (**SOL**), and *longissimus dorsi* (**LD**) muscle groups were weighed, and samples of each were collected for proximate analysis (Midwest Laboratories, Omaha, NE, USA) and immunohistochemistry.

Blood Sampling and IGF-1 ELISA.

Blood samples were collected on d -1, 3, and 30 by jugular venipuncture using EDTA-coated vacutainers (Greiner Bio-One, Monroe, NC) as previously described (Swanson et al., 2020). Plasma was separated by centrifuge (1,500 x *g*, 15 min) and stored at -80°C. Plasma concentrations of insulin-like growth factor 1 (**IGF-1**) were determined by commercial ELISA (Human IGF-1; ALPCO, Salem, NH, USA) that was previously validated for sheep (Brown et al., 2012).

Estimated and Actual Muscle Size and Body Composition.

Ultrasonic images of the loin were obtained on d 0, 14, and 30 to estimate loin-eye area (**LEA**), loin depth, and subcutaneous fat thickness as previously described (Swanson et al., 2020). Images were generated using an Ibex Pro ultrasound (E.I. Medical Imaging, Loveland, CO, USA), with the probe placed between the 12^{th} and 13^{th} right-side ribs, ~4 cm off the dorsal midline. Vegetable oil was used as a couplant. Measurements were obtained with the Ibex Pro system line and area functions by two independent technicians after images were de-identified. Four images were collected for each assessment and measurements from these images were averaged.

BIA was performed on live lambs on d -2, 2, 7, 14, 21, and 30 and on hot carcasses at necropsy. A four-terminal Quantum V (RJL Systems, Detroit, MI, USA) was used to measure tissue reactance, resistance, and phase angle as previously described (Gibbs et al., 2019). For live lambs, outer transmitter electrodes were placed 1 cm caudal to the scapula and 1 cm cranial to the iliac crest just to the right of the dorsal midline. Inner detection electrodes were placed 4 cm inside the outer electrodes. For the hot carcasses, electrodes were placed directly into the LD muscle at the same approximate positions as in the live lambs. Distance between detector electrodes was recorded, and 5 consecutive pulses were performed, averaged, and used to estimate kg of fat-free mass (**FFM**), fat-free soft tissue (**FFST**), and the combined mass of the leg, sirloin, and loin (**LSL**), the leg, sirloin, loin, rack, and shoulder (**LSLRS**), and the leg, sirloin, rack, shoulder, neck, riblets, shank, and lean trim (**SUM**) as previously described (Berg and Marchello, 1994; Gibbs et al., 2019).

Four-rib cutouts were isolated from the 9th to 12th ribs as previously described (Swanson et al., 2020). Cutouts were dissected into muscle, fat, bone, and connective tissue components, each of which were weighed. Proximate analyses were performed (Midwest Laboratories Inc., Omaha, NE, USA) on ST, BF, GAST, FDS, and LD muscles collected at necropsy to determine average moisture, protein, fat, ash, and carbohydrate content. Caloric values were also determined.

Immunohistochemistry.

Samples of ST muscle collected at necropsy were fixed in 4% paraformaldehyde (Sigma-Aldrich, St. Louis, MO, USA) that was dissolved in phosphate-buffered saline (**PBS**; Fisher Scientific, Fair Lawn, NJ, USA). Muscle samples were then embedded in OCT compound (Scigen Scientific, Gardena, CA, USA) and stored at -80°C as previously described (Yates et al., 2016). Three 10-µm cross sections from each animal were prepared using a CryoStar NX50 cryostat **(**Richard-Allan Scientific, Kalamazoo, MI, USA), mounted on Superfrost Plus microscope slides (Fisher Scientific, Pittsburgh, PA, USA), and stained using the process described by Yates et al. (2016), with some minor modifications. In the present study, antiserum raised in the mouse against desmin (GTX26322, 1:100; GeneTex, Irvine, CA, USA) was used to identify muscle fibers. Antiserum raised in the mouse against pax7 (PAX7, 1:10; DSHB, Iowa City, IA, USA) and myogenin (F5D**,** 1:10**;** DSHB) and antiserum raised in the rabbit against proliferating cell nuclear antigen (**PCNA**; CPTC-PCNA-1**,** 1:10**;** DSHB) were used to assess myoblast population profiles. Immunocomplexes were detected with Alexa Fluor 488, Alexa Fluor

555, or Alexa Fluor 594 (1:1000; Invitrogen Life Technologies, Carlsbad, CA, USA). Total nuclei were identified by 4',6-diamidino-2-phenylindole (**DAPI**; Fluoromount-G; Southern Biotech, Birmingham, AL, USA). Fluorescent images were visualized using an Olympus IX73 microscope (Olympus Corporation, Shinjuku, Tokyo, Japan) and digitally captured using an Olympus DP80 camera. Images were analyzed with Olympus cellSense Dimension 1.13 software. Average muscle fiber cross-sectional area was estimated from a minimum of 300 desmin$^+$ muscle fibers per animal. Percentages of pax7$^+$, pax7$^+$/PCNA$^+$, and myogenin$^+$ nuclei were determined from a minimum of 1,500 total nuclei per animal.

Statistical Analysis

Data collected over the feeding period were analyzed using the mixed procedure of SAS 9.4 (SAS Institute, Cary, NC, USA) with repeated measures to assess the fixed effects of experimental group, day, and their interaction. Fisher's LSD test was used for mean separation. Best-fit statistics were used to select appropriate covariance structures. Data collected at necropsy were analyzed by one-way ANOVA using the mixed procedure of SAS to assess the fixed effects of experimental group using lamb as the random effect. Lamb was considered the experimental unit for all analyses. Values are expressed as least squares means ± standard error.

RESULTS

Growth Biometrics.

Initial bodyweight and average daily feed intake did not differ among experimental groups by design (**Figure 2.1** and **Figure 2.2**). Final bodyweight, ADG, and G:F were less ($P < 0.05$) for heat-stress lambs but not heat stress+DEX or heat stress+fish oil than for controls. Empty bodyweight did not differ among groups. ST mass tended to be less ($P = 0.10$) for heat stress and heat stress+fish oil lambs but not heat stress+DEX lambs compared to controls (**Table 2.1**). BF mass tended to be less ($P = 0.07$) for heat stress but not heat stress+DEX or heat stress+fish oil compared to controls. GAST mass did not differ between controls and heat stress lambs but tended to be less ($P = 0.06$) for heat stress+fish oil lambs. FDS mass did not differ among groups. LD mass tended to be less ($P = 0.06$) for heat stress and heat stress+fish oil lambs but not heat stress+DEX lambs than for controls. SOL mass was less ($P < 0.05$) for heat stress lambs but not heat stress+DEX or heat stress+fish oil compared to controls.

ST/final bodyweight did not differ between controls and heat stress lambs but was less ($P < 0.05$) for heat stress+DEX and heat stress+fish oil lambs. BF/final bodyweight was less ($P < 0.05$) for heat stress lambs but not heat stress+DEX or heat stress+fish oil lambs compared to controls. GAST/final bodyweight and FDS/final bodyweight did not differ among groups. LD/final bodyweight did not differ between controls and heat stress lambs but was less ($P < 0.05$) for heat stress+DEX and heat stress+fish oil lambs. SOL/final bodyweight was less ($P < 0.05$) for heat stress and heat stress+DEX lambs but not heat stress+fish oil lambs compared to controls. ST/empty bodyweight was less ($P <$

0.05) for heat stress, heat stress+DEX, and heat stress+fish oil lambs than for controls. BF/empty bodyweight was less ($P < 0.05$) for heat stress lambs but not heat stress+DEX or heat stress+fish oil lambs than for controls. GAST/empty bodyweight did not differ between controls and heat stress lambs but was less ($P < 0.05$) for heat stress+fish oil lambs. FDS/empty bodyweight did not differ among groups. LD/empty bodyweight was less ($P < 0.05$) for heat stress but not heat stress+DEX lambs than for controls, and was less ($P < 0.05$) for heat stress+fish oil lambs than for all other groups. SOL/empty bodyweight was less ($P < 0.05$) for heat stress but not heat stress+fish oil lambs and was intermediate for heat stress+DEX lambs compared to controls.

Muscle Size and Body Composition.

Ultrasonic measurements. Experimental group x day interactions were observed ($P < 0.05$) for LEA and loin depth but not for fat thickness. At d 0, ultrasound-estimated LEA did not differ among groups (**Table 2.2**). At d 14 and 30, LEA were smaller ($P < 0.05$) for heat stress and heat stress+fish oil lambs but not heat stress+DEX lambs than for controls. At d 0, ultrasound-estimated loin depth did not differ among groups (**Table 2.2**). At d 14, loin depth was less ($P < 0.05$) for heat stress lambs but not heat stress+DEX or heat stress+fish oil lambs than for controls. At d 30, loin depth was less ($P < 0.05$) for heat stress but not heat stress+DEX lambs than for controls and was intermediate for heat stress+fish oil. Ultrasound-estimated backfat thickness was less ($P < 0.05$) for heat stress lambs than for controls and intermediate for heat stress+DEX and heat stress+fish oil (**Table 2.2**).

BIA measurements. Experimental group x day interactions were observed ($P < 0.05$) for all BIA estimates except LSLRS. Estimates for FFM and FFST by individual algorithms are presented in **Table 2.3** and **Table 2.4**. At d -2, 2, and 14, average BIA-estimated FFM did not differ among groups. At d 7, FFM was less ($P < 0.05$) for heat stress and heat stress-fish oil lambs but not heat stress+DEX lambs than for controls. At d 21, FFM was less ($P < 0.05$) for heat stress, heat stress+DEX, and heat stress+fish oil lambs than for controls. At 30, FFM did not differ between controls and heat stress lambs but was greater ($P < 0.05$) for heat stress+DEX and heat stress+fish oil lambs. At necropsy, hot carcass FFM was less ($P < 0.05$) for heat stress but not heat stress+DEX lambs than for controls and was intermediate for heat stress+fish oil lambs. At d -2 and 14, average BIA-estimated FFST did not differ among groups. At d 2, FFST was less ($P < 0.05$) for heat stress lambs but not heat stress+DEX or heat stress+fish oil lambs than for controls. At d 7, FFST was less ($P < 0.05$) for heat stress and heat stress+fish oil lambs but not heat stress+DEX lambs than for controls. At d 21, FFST was less ($P < 0.05$) for heat stress, heat stress+DEX, and heat stress+fish oil lambs than for controls. At d 30, FFST did not differ between controls and heat stress lambs but was greater ($P < 0.05$) for heat stress+DEX and heat stress+fish oil lambs. At necropsy, hot carcass FFST was less ($P < 0.05$) for heat stress lambs but not heat stress+DEX or heat stress+fish oil lambs than for controls. At d -2, BIA-estimated LSL did not differ among groups (**Table 2.5)**. At d 2, 7, and 14, LSL was less ($P < 0.05$) for heat stress lambs but not heat stress+DEX or heat stress+fish oil lambs than for controls. At d 21, LSL was less ($P < 0.05$) for heat stress and heat stress+DEX lambs but not heat stress+fish oil lambs than

for controls. At d 30, LSL did not differ between controls and any other group but was greater ($P < 0.05$) for heat stress+DEX and heat stress+fish oil lambs than for heat stress lambs. At necropsy, hot carcass LSL was less ($P < 0.05$) for heat stress lambs but not heat stress+DEX or heat stress+fish oil lambs than for controls. BIA-estimated LSLRS was less ($P < 0.05$) for heat stress and heat stress+DEX lambs but not heat stress+fish oil lambs than for controls, regardless of day. At d -2 and 14, BIA-estimated SUM was less ($P < 0.05$) for heat stress and heat stress+DEX lambs but not heat stress+fish oil lambs than for controls. At d 2 and 21, SUM was less ($P < 0.05$) for heat stress and heat stress+DEX lambs than for controls and was intermediate for heat stress+fish oil lambs. At d 7, SUM was less ($P < 0.05$) for heat stress lambs than controls and intermediate for heat stress+DEX and heat stress+fish oil lambs. At d 30, SUM was less ($P < 0.05$) for heat stress lambs but not heat stress+fish oil lambs than for controls and was intermediate for heat stress+DEX lambs. At necropsy, hot carcass SUM was less ($P < 0.05$) for heat stress lambs than for controls and was intermediate for heat stress+DEX and heat stress+fish oil lambs.

Four-Rib Cutout Composition. The percentage of muscle comprising the 4-rib cutout was less ($P < 0.05$) for heat stress and heat stress+fish oil lambs but not heat stress+DEX lambs than for controls (**Figure 2.3**). The percentage of fat and the percentage of bone comprising the cutout did not differ among experimental groups.

Proximate Analysis of Muscles. An experimental group x muscle interaction was observed ($P < 0.05$) for ash content but not for any other proximate analysis component. Moisture content did not differ among experimental groups and was greatest ($P < 0.05$) in FDS and GAST (**Table 2.6** and **Table 2.7**). Protein content was less ($P < 0.05$) for heat stress, heat stress+DEX, and heat stress+fish oil lambs than for controls, regardless of muscle type. Protein content was also greatest ($P < 0.05$) in FDS and LD and was least ($P < 0.05$) in BF and ST, regardless of experimental group. Fat content and fat-to-protein ratios were greater ($P < 0.05$) for heat stress, heat stress+DEX, and heat stress+fish oil lambs than for controls, regardless of muscle type. Fat content was also greatest ($P < 0.05$) in BF, GAST, and ST, regardless of experimental group. In BF, ash content was less ($P < 0.05$) for heat stress, heat stress+DEX, and heat stress+fish oil than for controls. In ST, ash content was less ($P < 0.05$) for heat stress lambs but not heat stress+fish oil lambs than for controls and was greater ($P < 0.05$) for heat stress+DEX than for controls. Ash content in FDS, GAST, and LD did not differ among groups. Carbohydrate content was less ($P < 0.05$) for heat stress and heat stress+DEX lambs but not heat stress+fish oil lambs than for controls, regardless of muscle type. Caloric content was greater ($P < 0.05$) for heat stress, heat stress+DEX, and heat stress+fish oil lambs than for controls, regardless of muscle type. Caloric content was also greatest ($P < 0.05$) in BF, GAST, and ST, regardless of experimental group.

Histological and Biochemical Analyses.

Muscle fiber size and myoblast profiles. The average cross-sectional area of *semitendinosus* muscle fibers was less ($P < 0.05$) for heat stress, heat stress+fish oil, and heat stress+DEX lambs than for controls (**Figure 2.4**). The percentage of total ST nuclei that were $pax7^+$ was not different among groups (**Figure 2.5**). The percentage of $pax7^+$ nuclei that were also $PCNA^+$ was not different among groups. The percentage of total nuclei that were $myogenin^+$ tended to be less ($P < 0.10$) for heat stress lambs but not heat stress+DEX lambs than for controls and tended to be intermediate for heat stress+fish oil lambs.

Plasma IGF-1 concentrations. Inter-assay and intra-assay coefficients of variation were less than 20%. No experimental group x day interaction was observed for plasma concentrations of IGF-1. Plasma IGF-1 concentrations did not differ among experimental groups but were less ($P < 0.05$) at d 3 than at d -1 or d 30, regardless of experimental group (**Figure 2.6**).

DISCUSSION

In this study, we showed that several negative effects of chronic heat stress on growth efficiency and body composition of feedlot lambs were mitigated by supplementing anti-inflammatory agents. Exposure to heat stress for 30 days decreased growth rates, muscle mass, and feed efficiency of wethers, despite the effects of differential feed intake being eliminated by pair feeding. Heat-stressed lambs were characterized by smaller ultrasound-estimated loin size after as little as two weeks of heat

stress. After a month, these lambs exhibited reduced BIA-estimated whole-body lean tissue mass as well as lighter muscles with less protein content, smaller fibers, and more non-muscle tissue components. Their decreased ultrasound-estimated subcutaneous fat thickness together with increased inter/intramuscular fat percentages for multiple muscles indicated changes in the nature of fat deposition during heat stress. We previously found that systemic inflammation was a mediator of heat stress effects (Barnes et al., 2019; Swanson et al., 2020; Barnes et al., 2021), and plasma TNFα in the present study was elevated 34% by heat stress throughout the study (Grijalva, Most, and Yates, unpublished). Targeting heat stress-induced inflammation with dexamethasone injections or oral fish oil boluses in the present study was effective in improving many but not all deficits in growth, feed efficiency, muscle mass, and fat deposits, although only fish oil moderated high circulating TNFα concentrations (Grijalva, Most, and Yates, unpublished). Moreover, myoblast population dynamics indicated conserved proliferation but reduced differentiation of these muscle stem cells in heat-stressed lambs, which would be consistent with enhanced inflammation. Indeed, targeting inflammation in heat-stressed lambs recovered indicators of myoblast differentiation. Surprisingly, circulating IGF-1 concentrations were not affected by heat stress or by the use of anti-inflammatory agents. Together, these findings demonstrate that heat stress-induced inflammation contributes to deficits in growth and body composition and that anti-inflammatory agents could be effective therapeutic options for improving these metrics in heat-stressed livestock.

Chronic heat stress reduced growth efficiency by mechanisms unrelated to nutritional intake. One such mechanism implicated by the present study is sustained systemic inflammation. By targeting inflammation, we were able to recover heat stress-impaired growth rates to the levels observed in pair-fed counterparts not exposed to heat stress. Decreased feed intake is in large part a behavioral adaptation that reduces the contribution of metabolic heat to an animal's heat load (Gaughan and Mader, 2009). However, this also limits the macromolecule substrates available for tissue growth. To illustrate, heat stress reduced average daily gain by 51% in a previous lamb study in which pair-feeding was not used to control for differential nutrient intake (Barnes et al., 2019). In the present study, we observed only a 23% reduction in average daily gain due to heat stress when thermoneutral controls were pair fed, which like our previous findings (Swanson, 2020) demonstrates mechanisms for growth dysfunction beyond reduced feed intake. Moreover, the implications of increasing metabolic heat in heat-stressed animals makes attempting to maintain weight gain and efficiency by offering more feed unreasonable. Thus, identifying this underlying role of enhanced inflammation is critical for developing alternative intervention strategies. Inflammatory signals help regulate normal muscle growth, but excessive exposure is detrimental to these processes (Kubik et al., 2018; Posont et al., 2018; Reith et al., 2020). By supplementing dexamethasone and fish oil, which are known to target inflammatory processes (Rhen and Cidlowski, 2005; Bennett and Gilroy, 2016), we were able to recover average daily gain of heat-stressed lambs, resulting in final bodyweights at necropsy that were comparable to unstressed lambs. However, neither the reduced growth rates due to heat stress nor the recovery due

to supplement appeared dependent upon circulating IGF-1 concentrations, as no differences were observed. This was unexpected, as Rhoads et al. (2010) found that heat stress in dairy cattle directly depressed circulating IGF-1 independent of changes in growth hormone (**GH**) concentrations and utilization of pair-feeding. However, a study of feedlot steers indicated that undernutrition altered the ability of GH to stimulate release of IGF-1 (Elsasser et al., 1989). Furthermore, heat stress suppresses thyroid axis hormones (Horowitz, 2001) that would normally activate GH and IGF-1 (Näntö-Salonen et al., 1993). Therefore, it is possible that circulating IGF-1 concentrations in our study were not different due to pair-feeding, which eliminated the mechanism of undernutrition, and that *ad libitum* feeding of unstressed controls would have revealed differential IGF-1 concentrations. Unlike final live bodyweights, we did not observe differences in empty bodyweights. Although unexpected given the differences in live weights, this was presumably an effect of the random sequence in which animals were necropsied, which affected the length of time they retained access to feed. Due to facility and personnel constraints, this potential limitation was unavoidable.

Like growth rates, feed efficiency was also impaired by heat stress independent of feed intake. By recovering it with dexamethasone and fish oil, we showed that systemic inflammation was a mediator of this deficit as well. Heat stress alters cellular utilization and metabolism of glucose and other nutrient substrates (Belhadj Slimen et al., 2016). A previous study by our lab demonstrated that chronic heat stress induced hyperinsulinemia, which is indicative of insulin resistance, and impaired skeletal muscle glucose oxidation (Barnes et al., 2019). A subsequent study confirmed these glucose

oxidation deficits even when pair feeding was used to eliminate nutritional effects and despite no effect of heat stress on skeletal muscle glucose uptake rates (Swanson et al., 2020). Furthermore, Sieck et al. (2021) found enriched gene expression for mitochondrial glycerol 3-phosphate dehydrogenase (*GPD2)* in heat-stressed lambs, which has been shown to limit glucose oxidation in response to chronic inflammation (Langston et al., 2019). Therefore, we speculate that administering anti-inflammatory agents in the present study reduced skeletal muscle *GPD2*, which restored glucose oxidation capacity and, in turn, metabolic efficiency. Additionally, skin blood flow is increased during heat stress, which enhances evaporative cooling but is detrimental to the digestive processes of the gastrointestinal tissues (Bell et al., 1983). Although we did not assess blood flow, it is possible that our administration of dexamethasone or fish oil to heat-stressed lambs improved efficiency of nutrient absorption and transport to growing tissues by reducing inflammatory tone and restoring blood flow to digestive organs.

Body composition assessments indicated impacts of heat stress on skeletal muscle-specific growth and on fat deposition, as well as inflammatory mediation for both. Live-animal estimations and postmortem measurements showed that muscle mass was decreased by heat stress, and targeting inflammation recovered size for several of the assessed muscles. Myoblast incorporation into existing myofibers increases protein synthesis capacity that muscle needs to grow (Allen et al., 1979; Lu et al., 2017). Consequently, muscle hypertrophy is rate-limited by the proliferation, differentiation, and fusion rates of myoblasts (Schmidt et al., 2019). We previously observed that exposure to inflammatory cytokines impaired myoblast progression from the proliferation stage to the

differentiation stage (Posont et al., 2018). In the present study, the similar percentages of ST pax7^{+} nuclei and pax7^{+}/PCNA^{+} nuclei among groups indicated no differences in the number of myoblasts present or their capacity to replicate. However, the decreased percentage of ST myogenin^{+} nuclei indicated a deficient capacity for myoblasts in heat-stressed lambs to differentiate. Moreover, full and partial recovery of ST myogenin^{+} nuclei associated with dexamethasone and fish oil supplementation, respectively, demonstrates the underlying inhibitory influence of heat stress-induced inflammation. Recovering the differentiation capacity of heat-stressed myoblasts led us to expect a consequential recovery of muscle fiber size, which was reduced 11% in ST from our heat-stressed lambs. However, we observed smaller muscle fibers in all heat-stressed lambs, including those supplemented with dexamethasone or fish oil. This unexpected observation reveals likely dysfunction of protein synthesis mechanisms that are downstream of myoblast differentiation (Chang et al., 2020) Additionally, the chronic use of exogenous glucocorticoids such as dexamethasone has been associated with muscle atrophy (Schakman et al., 2013), although there is a balance of positive anti-inflammatory effects and negative atrophic effects that are time- and dose-dependent (Crossland et al., 2010). This would explain the positive associations of dexamethasone administration with muscle mass in the present study. The lack of size recovery in some muscles likely reflects the variation in proportions of myofiber metabolic phenotypes, or fiber types (i.e., oxidative, glycolytic, intermediate), which are impacted differently by heat stress (Oishi et al., 2003). It may also be related to the functions of each muscle (e.g., postural vs. locomotive). Each fiber type also has distinct sensitivities to insulin and

stress hormones like adrenaline, creating the potential for differential growth outcomes (James et al., 1985; Martin et al., 1989).

In addition to decreased muscle size, heat-stressed lambs also exhibited changes in the composition of the muscles and in adipose deposition, which were only partially mediated by inflammation. Food animal carcasses are more valuable when they have a greater proportion of lean muscle and more intramuscular fat (i.e., marbling). Heat stress not only decreased loin size but also the protein content of the LD, which is the principal muscle comprising the loin, and muscle proportion of the 4-rib cutouts. Carcasses are also discounted for excess subcutaneous backfat and intermuscular fat, which is lost as trim waste. However, intermuscular fat proportions for 4-rib cutouts did not differ among groups, ultrasonic assessments indicated that heat stress decreased subcutaneous backfat thickness, and proximate analyses indicated that heat stress increased intramuscular fat content. It is worth noting that proximate analysis does not inherently distinguish between intramuscular and intermuscular fat (marbling and seam fat, respectively), and thus seam fat was carefully removed from muscles collected for proximate analysis. This loss of subcutaneous fat and gain of intramuscular fat appears to reflect reappropriation of adipose deposits. Indeed, fat deposition in heat-stressed animals has been shown to shift away from surface areas to internal stores to reduce insulating effect and improve heat exchange (Mader and Davis, 2004). Additional studies measuring abdominal fat mass would be warranted to confirm such changes in adipose deposition. Targeting inflammation partially reversed the effects of heat stress on subcutaneous backfat thickness but did not prevent heat stress-elevated intramuscular fat. In a similar study,

Reith et al. (2020) found that heat stress caused changes in the transcriptome of lamb adipose tissue that would be consistent with impaired fatty acid mobilization, including *RBM3* and *ATXN7L1* genes. Furthermore, heat stress can activate the adrenal axis and stimulates the release of glucocorticoids (Afsal et al., 2018). Campbell et al. (2011) showed that chronic exposure to elevated glucocorticoids caused net accumulation of visceral and intramuscular fat by promoting adipogenesis via preadipocyte differentiation despite also paradoxically promoting lipolysis in mature adipocytes. Our previous study found no differences in circulating cortisol concentrations between heat-stressed lambs and unstressed pair-fed lambs (Swanson et al., 2020), which we speculate was due at least in part to their equivalent nutritional plane. Urrutia et al. (2016) reported that supplementation of unstressed lambs with anti-inflammatory ω-3 polyunsaturated fatty acids resulted in larger subcutaneous adipocytes despite downregulation of lipogenic genes in subcutaneous adipose tissue, which may help explain the partial recovery of subcutaneous backfat thickness in our heat-stressed lambs supplemented with dexamethasone or fish oil.

The ability to quantify muscle mass in live animals prior to harvest could increase product uniformity and optimize profit by informing harvest times. Our findings showed that many of the differences in muscle growth and body composition documented postmortem were predicted in the live animal by ultrasonic and BIA estimates. For example, reduced size of loin muscles due to heat stress, their recovery by dexamethasone, and their lack of recovery by fish oil were all accurately predicted by ultrasonic measurements of the loin eye area performed the day before harvest. Similar

associations were observed between ultrasonic loin depth measurements and fractional LD mass. BIA estimates of fat-free lean mass closely resembled the changes in muscle percentage of 4-rib cutouts results. Although some predictions were less successful, most of the inaccuracies can be explained by differing contexts. For example, BIA estimations of fat-free mass were well-aligned with muscular protein content determined by proximate analysis because the former is a whole-body estimation and the latter is muscle-specific. Additionally, BIA estimations were generally more accurate when performed closer to necropsy, presumably due to greater disparities among groups. It is also worth noting that a previous study by our lab found that BIA estimates of body composition in younger animals can be more accurate when normalized to bodyweight (Gibbs et al., 2019). Although we did not measure actual backfat thickness, the reduction estimated by ultrasonography was consistent with the expected changes in lipid metabolism and mobilization that occur during heat stress (Belhadj Slimen et al., 2016).

CONCLUSIONS & IMPLICATIONS

From these results, we conclude that heat stress-induced inflammation plays a principal role in growth dysfunction independent of feed intake. Moreover, targeting systemic inflammation by persistent administration of the synthetic glucocorticoid dexamethasone or supplementation of the ω-3 polyunsaturated fatty acid-rich fish oil recovers much of the growth, feed efficiency, muscle mass, and body composition lost to heat stress. The ability of livestock producers to mitigate stress-associated welfare issues

and maintain a sustainable global food supply in the face of climate change is critical. By identifying and characterizing the underlying mechanisms whereby systemic inflammation reduce livestock growth efficiency, this study uncovers a potential target for non-nutritional therapies to recover performance and value of heat-stressed livestock.

Figure 2.1 Bodyweight metrics.

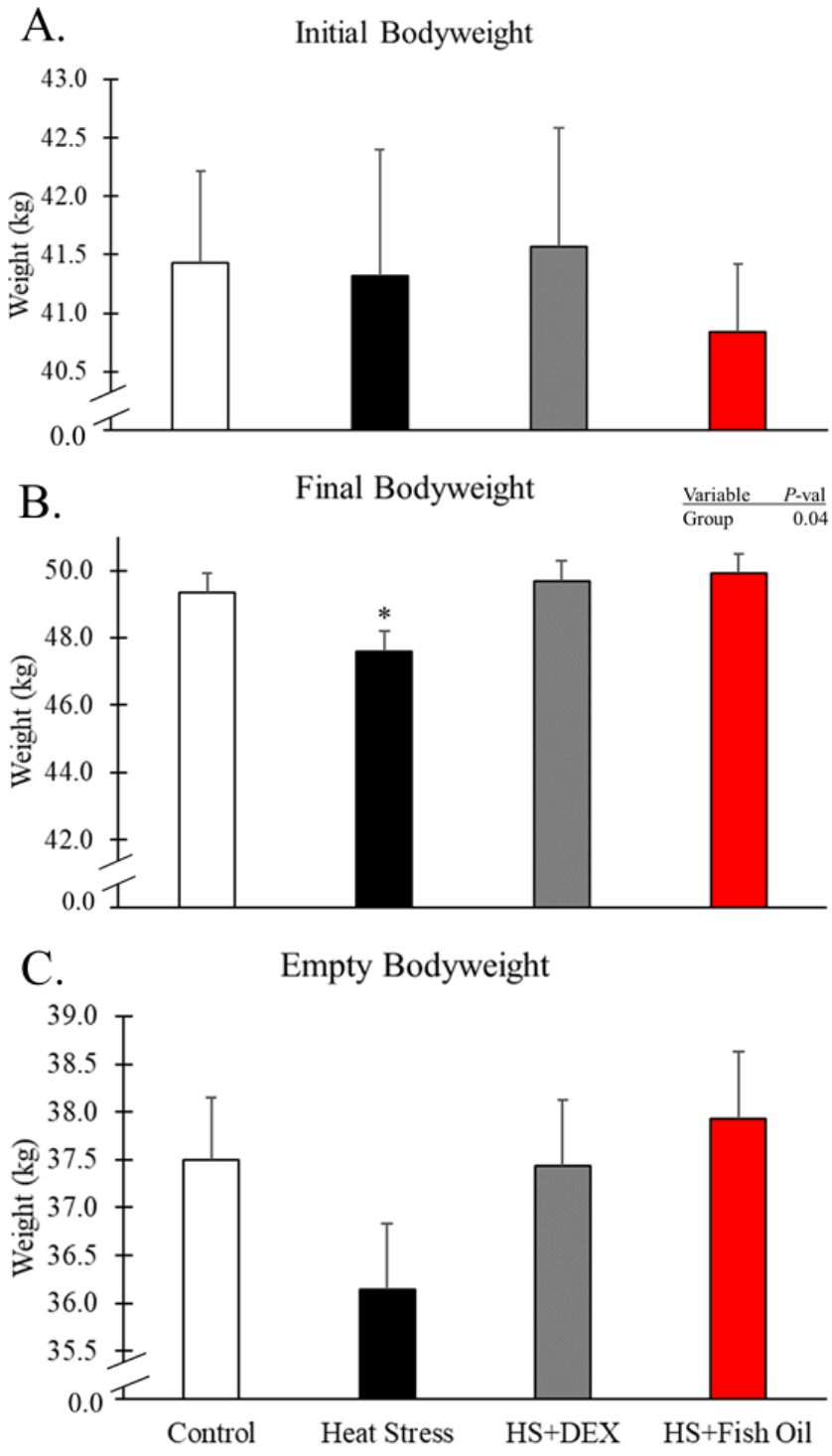

Figure 2.2 Growth and efficiency metrics.

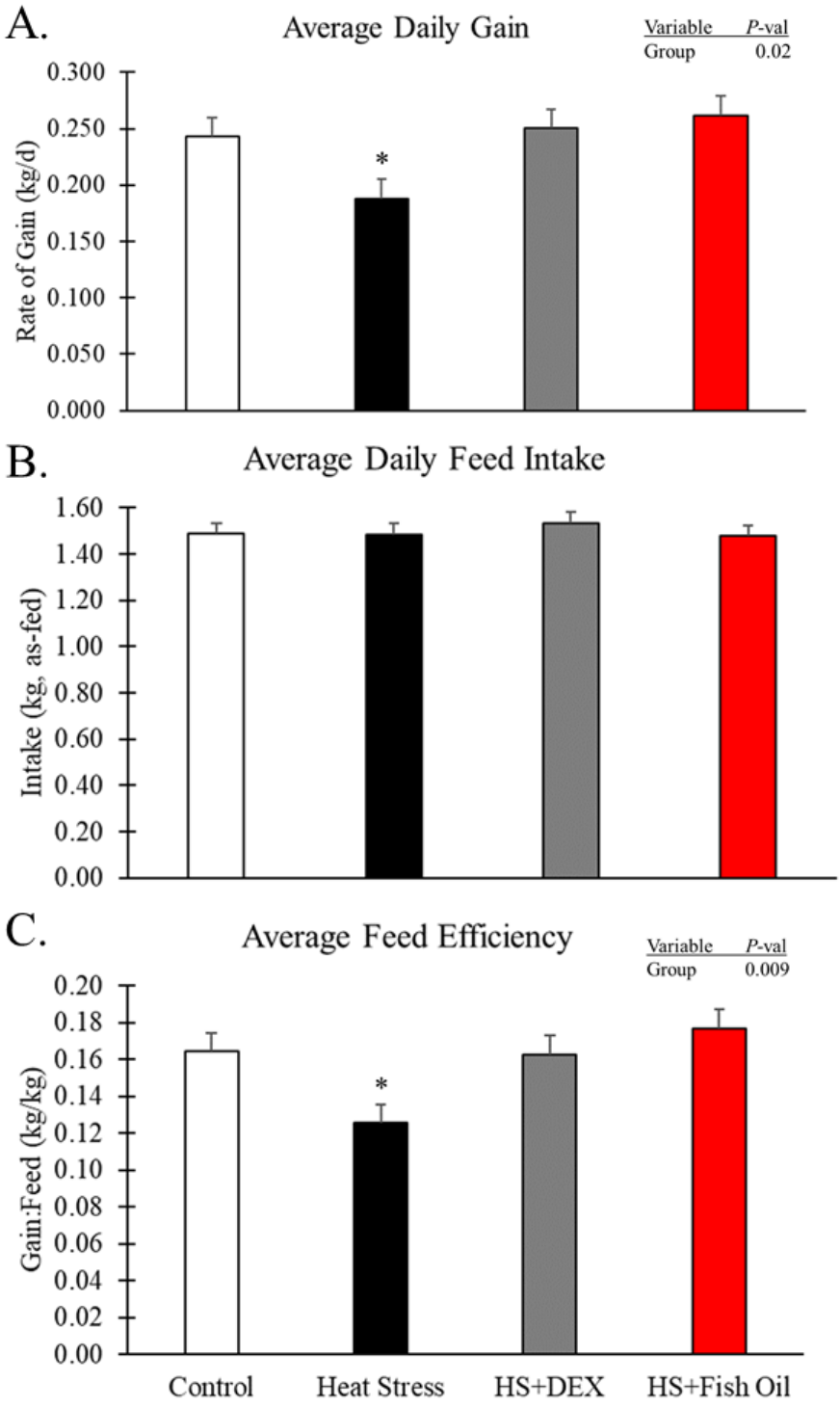

Figure 2.3 Four-rib cutout component parts.

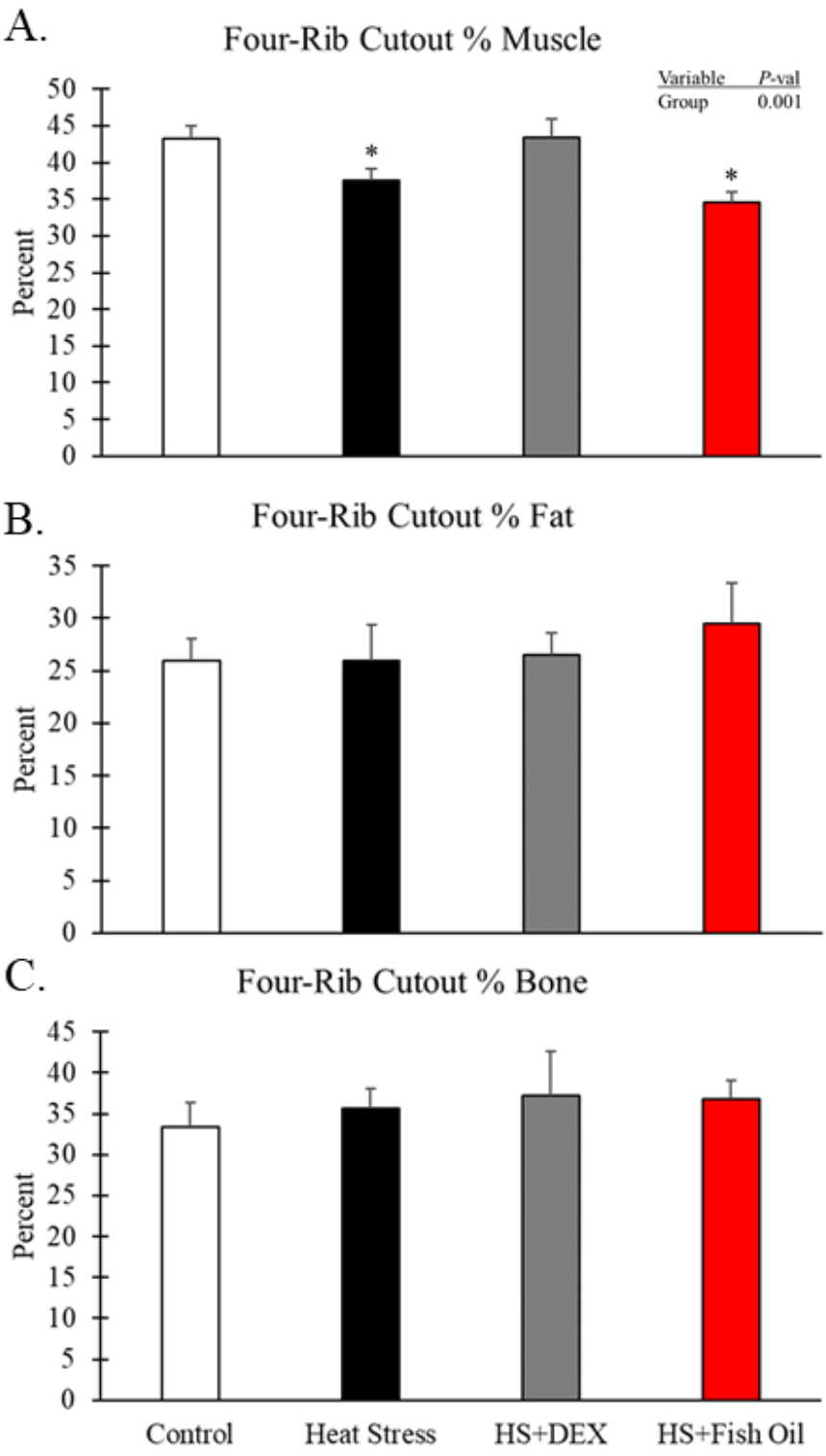

Figure 2.4 Average *semitendinosus* muscle fiber area.

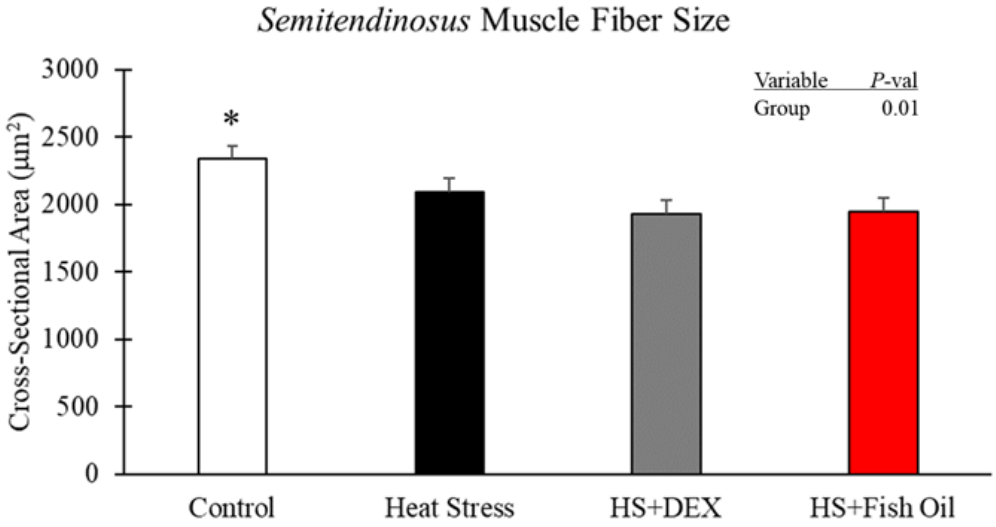

Figure 2.5 Myoblast profiles.

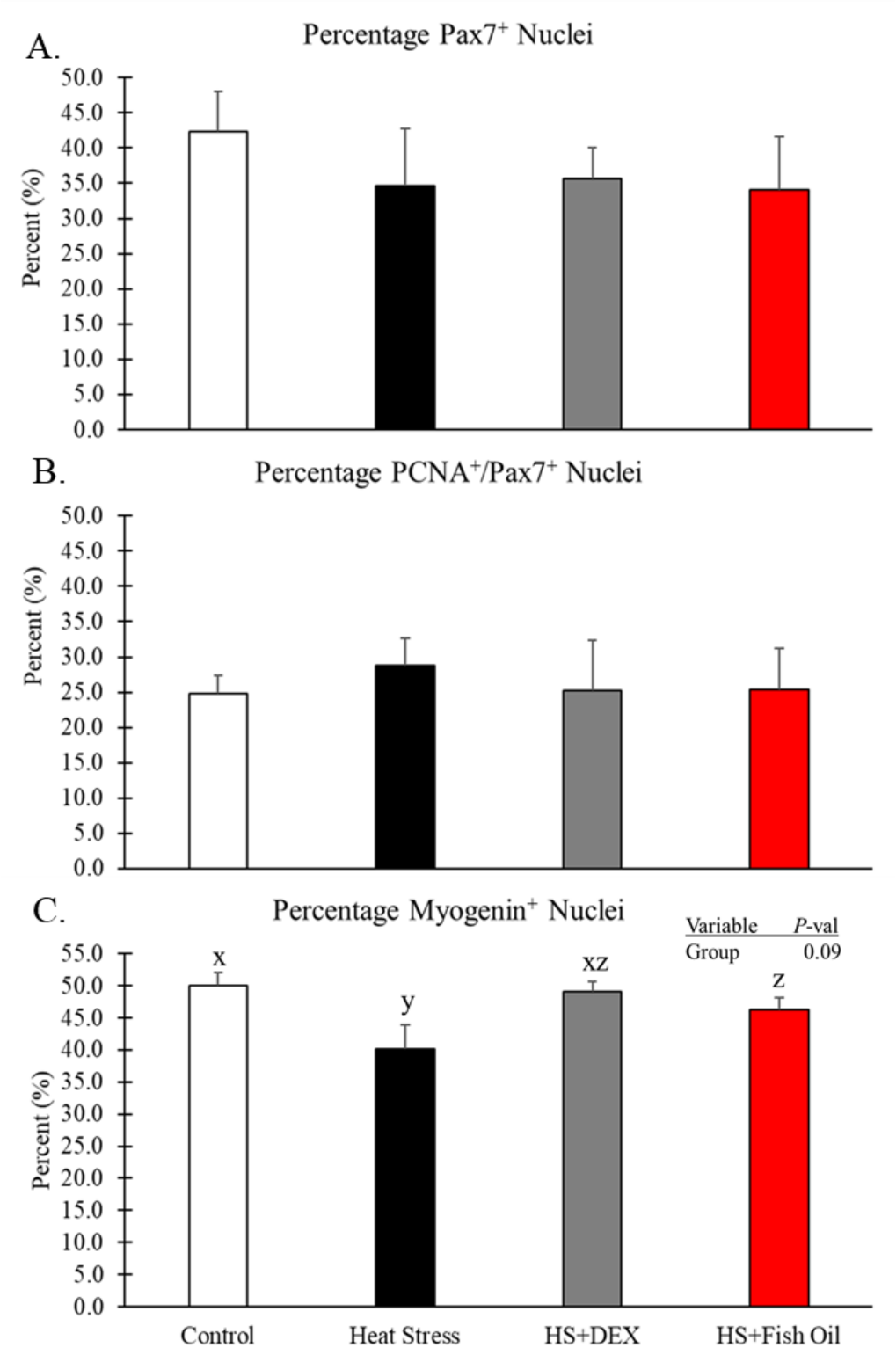

Figure 2.6 Plasma IGF-1 concentrations.

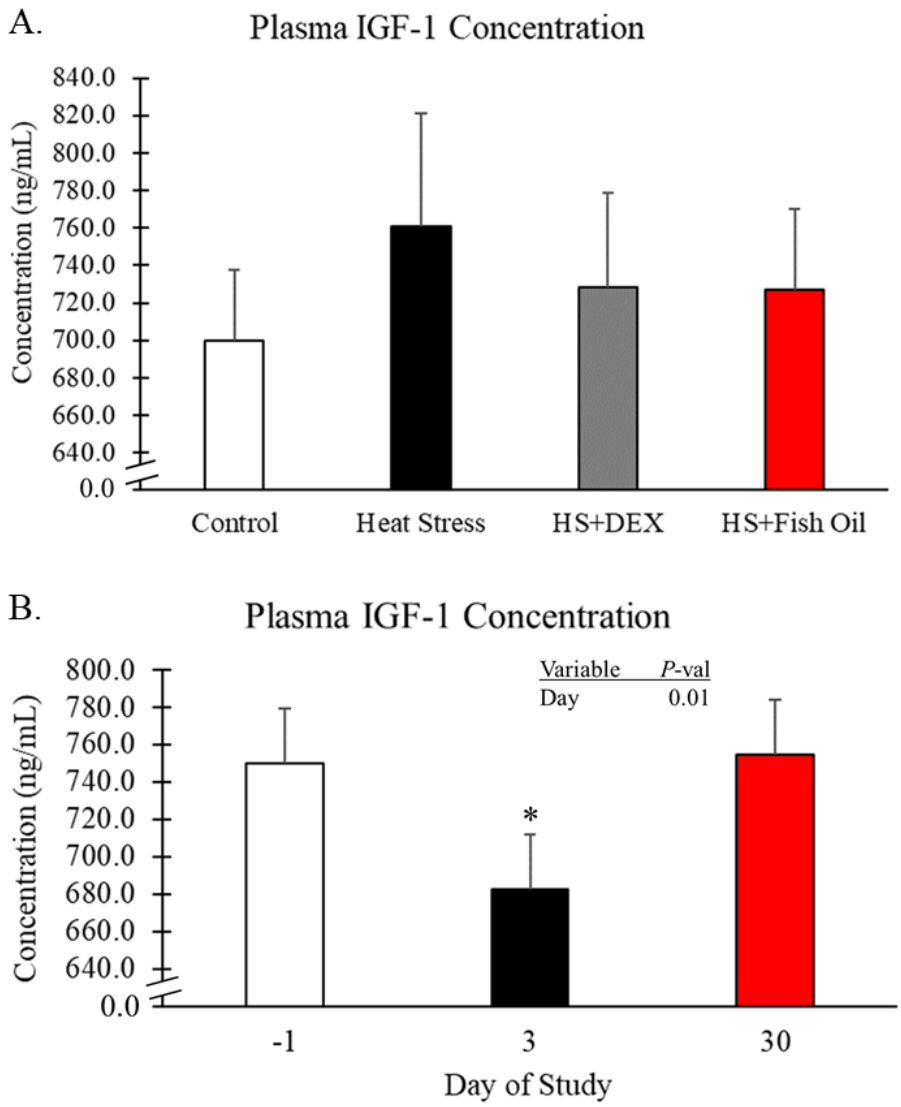

Table 2.1 Mass of skeletal muscles at necropsy.

Metric	Experimental Group				*P*-value
	Control	HS[1]	HS+DEX[2]	HS+FO[3]	
n	9	8	8	8	
Absolute Mass (g)					
Biceps femoris	403 ± 12^{x}	371 ± 10^{y}	403 ± 7^{x}	399 ± 11^{x}	0.07
Flexor digitorum superficialis	42 ± 1	41 ± 2	46 ± 2	41 ± 2	NS
Gastrocnemius	131 ± 4^{x}	127 ± 7^{xy}	135 ± 2^{x}	123 ± 4^{y}	0.06
Longissimus dorsi	660 ± 26^{x}	603 ± 29^{y}	616 ± 26^{xy}	572 ± 18^{y}	0.06
Soleus	2.66 ± 0.26^{a}	2.12 ± 0.15^{b}	2.60 ± 0.13^{a}	2.84 ± 0.32^{a}	0.05
Semitendinosus	145 ± 4^{x}	130 ± 5^{y}	135 ± 6^{xy}	134 ± 4^{y}	0.10
Mass/Final BW (g/kg)					
Biceps femoris	8.31 ± 0.16^{a}	7.77 ± 0.11^{b}	8.29 ± 0.14^{a}	8.22 ± 0.24^{a}	0.01
Flexor digitorum superficialis	0.89 ± 0.02	0.86 ± 0.03	0.93 ± 0.02	0.85 ± 0.04	NS
Gastrocnemius	2.66 ± 0.08	2.68 ± 0.09	2.72 ± 0.06	2.51 ± 0.07	NS
Longissimus dorsi	13.5 ± 0.4^{a}	13.2 ± 0.3^{a}	12.5 ± 0.2^{b}	12.1 ± 0.2^{b}	0.01
Soleus	0.064 ± 0.006^{a}	0.044 ± 0.004^{b}	0.049 ± 0.003^{b}	0.058 ± 0.006^{a}	0.05
Semitendinosus	2.98 ± 0.04^{a}	2.87 ± 0.11^{ab}	2.74 ± 0.06^{b}	2.75 ± 0.07^{b}	0.01
Mass/Empty BW (g/kg)					
Biceps femoris	10.88 ± 0.23^{a}	10.12 ± 0.23^{b}	10.91 ± 0.16^{a}	10.72 ± 0.25^{a}	0.05
Flexor digitorum superficialis	1.17 ± 0.03	1.11 ± 0.04	1.23 ± 0.03	1.15 ± 0.04	NS
Gastrocnemius	3.55 ± 0.11^{a}	3.48 ± 0.09^{ab}	3.61 ± 0.06^{a}	3.29 ± 0.08^{b}	0.03
Longissimus dorsi	17.8 ± 0.6^{x}	16.5 ± 0.4^{y}	16.8 ± 0.4^{xy}	15.4 ± 0.3^{z}	0.06
Soleus	0.081 ± 0.009^{a}	0.056 ± 0.004^{b}	0.066 ± 0.003^{c}	0.077 ± 0.007^{ac}	0.05
Semitendinosus	3.91 ± 0.06^{a}	3.73 ± 0.12^{b}	3.60 ± 0.10^{b}	3.57 ± 0.09^{b}	0.01

[a, b] Means with different superscripts differ ($P < 0.05$).
[x, y] Means with different superscripts tend to differ ($P < 0.10$).
[1] Heat stress with no intervention.
[2] Heat stress + Dexamethasone IM injection every 72 h.
[3] Heat stress + Fish oil oral bolus twice daily.
BW, bodyweight; NS, Not significant.

Table 2.2 Ultrasonic metrics.

Metric	Experimental Group				*P*-value		
	Control	HS[1]	HS+DEX[2]	HS+FO[3]	Group	Day	G*D[4]
n	9	8	8	8			
Loin eye area (mm^2)							
Day 0	1092 ± 25	1085 ± 29	1060 ± 34	1035 ± 31	---	---	NS
Day 14	1149 ± 23[a]	1057 ± 25[b]	1118 ± 26[a]	1057 ± 32[b]	---	---	0.001
Day 30	1159 ± 26[a]	1077 ± 30[b]	1125 ± 28[a]	1063 ± 24[b]	---	---	0.001
Loin depth (mm)							
Day 0	23.36 ± 0.29	23.64 ± 0.57	22.52 ± 0.44	23.25 ± 0.31	---	---	NS
Day 14	24.12 ± 0.27[a]	22.96 ± 0.44[b]	24.01 ± 0.38[a]	23.53 ± 0.52[ab]	---	---	0.04
Day 30	24.12 ± 0.31[ab]	22.94 ± 0.42[c]	24.33 ± 0.42[a]	23.49 ± 0.27[bc]	---	---	0.04
Fat thickness (mm)	2.48 ± 0.07[a]	1.85 ± 0.05[b]	2.21 ± 0.05[c]	2.05 ± 0.05[d]	< 0.001	NS	NS

[a, b, c, d] Means with different superscripts differ ($P < 0.05$).
[1] Heat stress with no intervention.
[2] Heat stress + Dexamethasone IM injection every 72 h.
[3] Heat stress + Fish oil oral bolus twice daily.
[4] Group by day interaction.
NS, Not significant.

Table 2.3 Bioelectrical impedance analysis estimates of fat-free mass.

Metric	Experimental Group				*P*-value		
	Control	HS[1]	HS+DEX[2]	HS+FO[3]	Group	Day	G*D[4]
n	9	8	8	8			
FFM1[5] (kg/kg BW)	32.4 ± 0.9^{ab}	30.5 ± 0.9^{c}	34.0 ± 1.0^{b}	31.4 ± 0.7^{ac}	0.07	< 0.001	NS
FFM2[6] (kg/kg BW)							
Day -2	26.9 ± 0.7	27.1 ± 1.6	28.9 ± 1.2	27.3 ± 1.0	NS	NS	NS
Day 2	28.4 ± 0.9^{a}	26.2 ± 1.2^{b}	28.6 ± 1.0^{a}	28.2 ± 1.0^{a}	---	---	0.005
Day 7	29.9 ± 0.9^{a}	28.1 ± 0.9^{b}	29.9 ± 1.1^{ab}	28.0 ± 1.0^{b}	---	---	0.005
Day 14	30.3 ± 0.8	30.0 ± 1.1	30.1 ± 1.3	30.8 ± 1.1	NS	NS	NS
Day 21	32.5 ± 0.9^{a}	27.8 ± 1.3^{b}	29.7 ± 1.0^{b}	30.0 ± 1.1^{b}	---	---	0.005
Day 30	29.7 ± 0.8^{a}	31.1 ± 1.1^{ab}	32.9 ± 0.8^{b}	32.5 ± 0.8^{b}	---	---	0.005
NEC	32.9 ± 0.6^{a}	30.5 ± 0.8^{b}	32.4 ± 0.7^{ac}	31.7 ± 0.5^{c}	---	---	0.005
FFM3[7] (kg/kg BW)							
Day -2	28.1 ± 0.7	28.4 ± 1.5	30.5 ± 1.2	28.5 ± 1.0	NS	NS	NS
Day 2	29.4 ± 0.9	27.5 ± 1.2	30.1 ± 1.0	29.5 ± 1.0	NS	NS	NS
Day 7	31.0 ± 0.9	29.3 ± 0.9	31.5 ± 1.1	29.4 ± 1.0	NS	NS	NS
Day 14	31.4 ± 0.8	31.4 ± 1.1	31.9 ± 1.3	32.2 ± 1.1	NS	NS	NS
Day 21	33.8 ± 1.0^{a}	29.2 ± 1.3^{b}	31.2 ± 1.0^{b}	31.2 ± 1.1^{b}	---	---	0.002
Day 30	31.5 ± 0.8	32.5 ± 1.3	34.6 ± 1.1	33.8± 0.7	NS	NS	NS
NEC	33.7 ± 0.6	32.1 ± 0.8	34.0 ± 0.5	32.9 ± 0.4	NS	NS	NS
FFM4[8] (kg/kg BW)							
Day -2	26.6 ± 0.6	25.9 ± 0.5	25.3 ± 0.9	25.3 ± 0.4	NS	NS	NS
Day 2	26.3 ± 0.7^{a}	26.2 ± 0.4^{a}	25.3 ± 1.0^{a}	23.1 ± 0.8^{b}	---	---	< 0.001
Day 7	29.1 ± 0.7^{a}	27.3 ± 0.6^{b}	27.2 ± 0.9^{b}	25.9 ± 1.1^{b}	---	---	< 0.001
Day 14	30.3 ± 0.6^{a}	28.8 ± 0.8^{b}	29.1 ± 1.0^{ab}	27.0 ± 1.1^{b}	---	---	< 0.001
Day 21	32.4 ± 0.6^{a}	28.7 ± 0.8^{b}	27.8 ± 0.8^{bc}	26.9 ± 0.8^{c}	---	---	< 0.001
Day 30	30.9 ± 0.8^{a}	30.0 ± 0.8^{ab}	31.0 ± 0.7^{a}	28.9 ± 0.9^{b}	---	---	< 0.001
NEC	38.2 ± 0.7^{a}	34.7 ± 1.0^{b}	36.3 ± 0.9^{c}	31.4 ± 1.6^{d}	---	---	< 0.001
Mean FFM[9] (kg/kg BW)							
Day -2	27.8 ± 0.9	28.1 ± 1.5	30.2 ± 1.2	27.9 ± 1.0	NS	NS	NS
Day 2	28.8 ± 0.9	27.0 ± 1.3	29.2 ± 1.0	28.4 ± 0.9	NS	NS	NS
Day 7	30.8 ± 0.9^{a}	28.9 ± 1.1^{b}	30.7 ± 1.3^{ab}	28.8 ± 0.8^{b}	---	---	< 0.001
Day 14	31.3 ± 0.7	31.1 ± 1.2	30.4 ± 1.6	31.8 ± 0.9	NS	NS	NS
Day 21	33.3 ± 0.8^{a}	28.9 ± 1.3^{b}	29.6 ± 1.2^{b}	30.8 ± 1.2^{b}	---	---	< 0.001
Day 30	30.6 ± 0.8^{a}	31.6 ± 1.2^{a}	33.0 ± 1.0^{b}	32.6 ± 0.9^{b}	---	---	< 0.001
NEC	34.4 ± 0.6^{a}	32.2 ± 0.8^{b}	33.7 ± 0.6^{ac}	33.2 ± 0.6^{bc}	---	---	< 0.001

[a, b, c, d] Means with different superscripts differ (P < 0.05).
[1] Heat stress with no intervention.
[2] Heat stress + Dexamethasone IM injection every 72 h.
[3] Heat stress + Fish oil oral bolus twice daily.
[4] Group by day interaction.
[5] Fat free mass 1.
[6] Fat free mass 2.
[7] Fat free mass 3.
[8] Fat free mass 4.
[9] Mean of fat free mass 1-4.
BW, Body weight; NS, Not significant; NEC, Necropsy.

Table 2.4 Bioelectrical impedance analysis estimates of fat-free soft tissue.

Metric	Experimental Group				*P*-value		
	Control	HS[1]	HS+DEX[2]	HS+FO[3]	Group	Day	G*D[4]
n	9	8	8	8			
FFST1[5] (kg/kg BW)							
Day -2	27.6 ± 0.9	27.6 ± 1.3	29.7 ± 1.1	27.5 ± 0.9	NS	NS	NS
Day 2	27.9 ± 0.9	26.9 ± 1.1	29.0 ± 0.9	27.7 ± 0.8	NS	NS	NS
Day 7	30.3 ± 0.9	28.7 ± 1.0	30.5 ± 1.1	28.8 ± 0.8	NS	NS	NS
Day 14	31.0 ± 0.7	30.6 ± 1.1	30.6 ± 1.4	31.5 ± 0.8	NS	NS	NS
Day 21	32.6 ± 0.7^{a}	28.8 ± 1.2^{b}	29.7 ± 1.2^{b}	30.3 ± 1.0^{b}	---	---	0.005
Day 30	30.6 ± 0.9	31.0 ± 1.1	32.4 ± 1.0	31.7 ± 0.9	NS	NS	NS
NEC	32.3 ± 0.7^{a}	30.1 ± 0.8^{b}	32.0 ± 0.5^{a}	31.2 ± 0.6^{ab}	---	---	0.005
FFST2[6] (kg/kg BW)							
Day -2	26.4 ± 0.8	26.4 ± 1.5	28.5 ± 1.1	26.5 ± 1.0	NS	NS	NS
Day 2	27.7 ± 0.8^{a}	25.3 ± 1.2^{b}	27.4 ± 1.0^{a}	27.1 ± 0.9^{a}	---	---	< 0.001
Day 7	29.2 ± 0.8^{a}	26.9 ± 1.0^{bc}	28.7 ± 1.1^{ac}	27.1 ± 0.8^{b}	---	---	< 0.001
Day 14	29.5 ± 0.7	29.0 ± 1.2	28.2 ± 1.5	29.7 ± 0.8	NS	NS	NS
Day 21	31.5 ± 0.8^{a}	26.9 ± 1.2^{b}	27.7 ± 1.1^{bc}	29.2 ± 1.1^{c}	---	---	< 0.001
Day 30	29.0 ± 0.7^{a}	29.8 ± 1.1^{b}	31.1 ± 0.9^{bc}	31.2 ± 0.9^{c}	---	---	< 0.001
NEC	31.5 ± 0.6^{a}	29.0 ± 0.7^{bc}	30.4 ± 0.6^{a}	30.3 ± 0.7^{ac}	---	---	< 0.001
FFST3[7] (kg/kg BW)							
Day -2	27.6 ± 0.8	27.6 ± 1.5	29.8 ± 1.1	27.8 ± 1.1	NS	NS	NS
Day 2	28.7 ± 0.8^{a}	26.4 ± 1.1^{b}	28.7 ± 1.0^{a}	28.4 ± 0.9^{a}	---	---	< 0.001
Day 7	30.3 ± 0.8^{a}	28.0 ± 1.0^{b}	30.0 ± 1.1^{ab}	28.5 ± 0.7^{b}	---	---	< 0.001
Day 14	30.7 ± 0.7	30.2 ± 1.3	29.8 ± 1.4	31.2 ± 0.8	NS	NS	NS
Day 21	32.9 ± 0.8^{a}	28.3 ± 1.2^{b}	29.3 ± 1.1^{b}	30.5 ± 1.1^{b}	---	---	< 0.001
Day 30	30.3 ± 0.8^{a}	31.4 ± 1.0^{ab}	32.8 ± 0.9^{b}	32.7 ± 0.9^{b}	---	---	< 0.001
NEC	30.1 ± 0.6^{a}	28.1 ± 0.8^{bc}	29.9 ± 0.4^{a}	29.2 ± 0.6^{ac}	---	---	< 0.001
Mean FFST[8] (kg/kg BW)							
Day -2	27.2 ± 0.8	27.3 ± 1.4	29.3 ± 1.1	27.3 ± 0.9	NS	NS	NS
Day 2	28.1 ± 0.8^{a}	26.2 ± 1.1^{bc}	28.3 ± 1.0^{a}	27.7 ± 0.8^{ac}	---	---	< 0.001
Day 7	29.9 ± 0.8^{a}	27.9 ± 1.0^{b}	29.7 ± 1.1^{ab}	28.1 ± 0.7^{b}	---	---	< 0.001
Day 14	30.4 ± 0.7	29.9 ± 1.2	29.4 ± 1.4	30.9 ± 0.8	NS	NS	NS
Day 21	32.3 ± 0.7^{a}	28.0 ± 1.2^{b}	28.8 ± 1.1^{b}	30.0 ± 1.1^{b}	---	---	< 0.001
Day 30	29.9 ± 0.8^{a}	30.7 ± 1.1^{ab}	32.1 ± 0.9^{b}	31.9 ± 0.8^{b}	---	---	< 0.001
NEC	31.3 ± 0.6^{a}	29.1 ± 0.8^{b}	30.7 ± 0.5^{a}	30.2 ± 0.6^{ab}	---	---	< 0.001

[a, b, c, d] Means with different superscripts differ ($P < 0.05$).
[1] Heat stress with no intervention.
[2] Heat stress + Dexamethasone IM injection every 72h.
[3] Heat stress + Fish oil oral bolus twice daily.
[4] Group by day interaction.
[5] Fat free soft tissue 1.
[6] Fat free soft tissue 2.
[7] Fat free soft tissue 3.
[8] Mean of fat free soft tissue 1-3.
[9] BW, body weight; NS, Not significant; NEC, Necropsy.

Table 2.5 Bioelectrical impedance analysis estimates of primal cut masses.

Metric	Experimental Group				*P*-value		
	Control	HS[1]	HS+DEX[2]	HS+FO[3]	Group	Day	G*D[4]
n	9	8	8	8			
LSLRS[5] (kg/kg BW)	11.1 ± 0.3[a]	10.0 ± 0.3[b]	10.4 ± 0.3[b]	10.9 ± 0.2[a]	0.02	< 0.001	NS
LSL[6] (kg/kg BW)							
Day -2	5.7 ± 0.2	5.4 ± 0.2	5.9 ± 0.2	5.8 ± 0.2	NS	NS	NS
Day 2	5.9 ± 0.2[a]	5.2 ± 0.2[b]	5.7 ± 0.2[a]	5.8 ± 0.1[a]	---	---	0.01
Day 7	6.3 ± 0.2[a]	5.3 ± 0.2[b]	6.0 ± 0.2[a]	6.0 ± 0.1[a]	---	---	0.01
Day 14	6.5 ± 0.2[a]	5.7 ± 0.3[b]	6.1 ± 0.2[ab]	6.6 ± 0.2[a]	---	---	0.01
Day 21	6.6 ± 0.2[a]	5.6 ± 0.3[b]	6.0 ± 0.2[bc]	6.3 ± 0.2[ac]	---	---	0.01
Day 30	6.8 ± 0.2[ab]	6.4 ± 0.3[b]	6.8 ± 0.2[a]	7.0 ± 0.2[a]	---	---	0.01
NEC	6.8 ± 0.2[a]	5.8 ± 0.3[b]	6.4 ± 0.2[a]	6.4 ± 0.2[a]	---	---	0.01
SUM[7] (kg/kg BW)							
Day -2	14.3 ± 0.3[a]	13.0 ± 0.4[b]	13.3 ± 0.4[bc]	13.9 ± 0.3[ac]	---	---	< 0.001
Day 2	14.6 ± 0.3[a]	12.8 ± 0.3[b]	13.2 ± 0.4[b]	13.9 ± 0.3[c]	---	---	< 0.001
Day 7	15.7 ± 0.4[a]	13.2 ± 0.4[b]	14.0 ± 0.4[c]	14.8 ± 0.3[d]	---	---	< 0.001
Day 14	16.0 ± 0.3[a]	14.2 ± 0.6[b]	14.6 ± 0.4[b]	16.0 ± 0.4[a]	---	---	< 0.001
Day 21	17.1 ± 0.4[a]	13.9 ± 0.5[b]	14.3 ± 0.3[b]	15.2 ± 0.4[c]	---	---	< 0.001
Day 30	17.1 ± 0.5[a]	15.4 ± 0.5[b]	16.3 ± 0.3[c]	16.9 ± 0.3[a]	---	---	< 0.001
NEC	17.1 ± 0.4[a]	14.2 ± 0.6[b]	15.4 ± 0.4[c]	15.9 ± 0.3[c]	---	---	< 0.001

[a, b, c, d] Means with different superscripts differ ($P < 0.05$).
[1] Heat stress with no intervention.
[2] Heat stress + Dexamethasone IM injection every 72 h.
[3] Heat stress + Fish oil oral bolus twice daily.
[4] Group by day interaction.
[5] Sum of leg, sirloin, loin, rack, and shoulder.
[6] Sum of leg, sirloin, and loin.
[7] Sum of leg, sirloin, rack, shoulder, neck, riblets, shank, and lean trim.
BW, Body weight; NS, Not significant; NEC, Necropsy.

Table 2.6 Proximate analysis results by muscle.

Metric	Muscle					*P*-values		
	BF[3]	FDS[4]	GAST[5]	LD[6]	ST[7]	Group	Muscle	G*M[8]
Moisture (%)	70.78 ± 0.33[a]	74.25 ± 0.33[b]	73.84 ± 0.33[b]	70.33 ± 0.33[c]	70.99 ± 0.33[c]	NS	< 0.001	NS
Protein (%)	19.30 ± 0.17[a]	19.75 ± 0.18[b]	19.61 ± 0.18[c]	20.67 ± 0.18[b]	19.44 ± 0.17[a]	0.03	< 0.001	NS
Fat (%)	7.11 ± 0.49[a]	5.96 ± 0.50[b]	6.74 ± 0.49[a]	5.86 ± 0.49[b]	6.71 ± 0.49[a]	0.04	< 0.001	NS
F:P[1]	0.378 ± 0.031[a]	0.335 ± 0.032[b]	0.368 ± 0.032[ac]	0.271 ± 0.031[d]	0.352 ± 0.031[bc]	0.001	< 0.001	NS
Ash (%)	---	---	---	---	---	---	---	0.003
CHO[2] (%)	0.73 ± 0.29	1.01 ± 0.30	0.64 ± 0.30	0.66 ± 0.29	1.00 ± 0.29	0.02	NS	NS
Calories	144.1 ± 3.1[a]	139.7 ± 3.1[b]	143.3 ± 3.1[a]	137.6 ± 3.1[b]	142.6 ± 3.1[a]	0.002	< 0.001	NS

[a,b,c,d] Means with different superscripts differ ($P < 0.05$).

[1] Percent fat to percent protein ratio.

[2] Carbohydrate.

[3] *Biceps femoris.*

[4] *Flexor digitorum superficialis.*

[5] *Gastrocnemius.*

[6] *Longissimus dorsi.*

[7] *Semitendinosus.*

[8] Group by treatment interaction.

NS, Not significant.

Table 2.7 Proximate analysis results by experimental group.

Metric	Experimental Group				*P*-value		
	Control	HS[3]	HS+DEX[4]	HS+FO[5]	Group	Muscle	G*M[6]
n	9	8	8	8			
Moisture (%)	71.76 ± 0.34	72.06 ± 0.40	72.92 ± 0.45	71.42 ± 0.46	NS	< 0.001	NS
Protein (%)	20.01 ± 0.15[a]	19.74 ± 0.16[b]	19.65 ± 0.16[b]	19.60 ± 0.16[b]	0.03	< 0.001	NS
Fat (%)	6.10 ± 0.48[a]	6.55 ± 0.48[b]	6.66 ± 0.48[b]	6.59 ± 0.48[b]	0.04	< 0.001	NS
F:P[1]	0.308 ± 0.030[a]	0.351 ± 0.031[b]	0.364 ± 0.031[b]	0.342 ± 0.031[b]	0.001	< 0.001	NS
Ash (%)							
Biceps femoris	1.05 ± 0.03[a]	0.98 ± 0.03[b]	0.98 ± 0.03[b]	0.96 ± 0.04[b]	---	---	0.003
Flexor digitorum superficialis	0.97 ± 0.03	0.99 ± 0.04	0.97 ± 0.04	0.95 ± 0.04	NS	NS	NS
Gastrocnemius	0.99 ± 0.03	1.01 ± 0.04	0.99 ± 0.04	0.98 ± 0.04	NS	NS	NS
Longissimus dorsi	1.02 ± 0.03	1.00 ± 0.04	1.02 ± 0.03	1.03 ± 0.04	NS	NS	NS
Semitendinosus	1.06 ± 0.03[a]	1.00 ± 0.04[b]	1.13 ± 0.03[c]	1.02 ± 0.04[ab]	---	---	0.003
CHO[2] (%)	1.09 ± 0.28[a]	0.60 ± 0.28[b]	0.68 ± 0.29[b]	0.87 ± 0.28[a]	0.02	NS	NS
Calories	138.5 ± 3.0[a]	142.6 ± 3.0[b]	143.1 ± 3.1[b]	141.6 ± 3.0[b]	0.002	<0.001	NS

[a, b, c, d] Means with different superscripts differ ($P < 0.05$) for each muscle.

[1] Percent fat to percent protein ratio.

[2] Carbohydrate.

[3] Heat stress with no intervention.

[4] Heat stress + Dexamethasone IM injection every 72 h.

[5] Heat stress + Fish oil oral bolus twice daily.

[6] Group by muscle interaction.

NS, Not significant.

CHAPTER 3 - A BRIEF EXPLORATION AND APPLICATION OF EXTENSION PRINCIPLES

ABSTRACT

The Cooperative Extension Service, created in 1914, facilitates interaction and communication between academics and the general public related to agriculture and public health. Agricultural extension services benefit producers of agricultural products and inform the research programs at land-grant universities. Extension methodology follows a general pattern that directs the flow of information, regardless of the discipline. This chapter describes the creative processes for written extension materials and digital media materials using a recently created NebGuide and an extension podcast as respective illustrations of the methodology in practice. Extension programming and content delivery via a broader range of modes will better ensure effective communication and assist extension professionals in reaching wider and more diverse audiences.

INTRODUCTION

The Morrill Act of 1862 established the US land-grant system for agriculture-based higher education with an explicitly stated objective: *the leading object shall be, without excluding other scientific and classical studies, and including military tactics, to teach such branches of learning as are related to agriculture and the mechanic arts* (Croft, 2019). To augment the teaching and research efforts enacted by this legislation, the Smith-Lever Act of 1914 created the Cooperative Extension Service to produce continuing-education programming and resources for agricultural producers (Fiske, 1989). Extension professionals work as liaisons between the public and those engaged in

scientific research, especially that related to sustainable agriculture and public health. In this way, agricultural extension systems like Nebraska Extension facilitate the transmission of information from researchers and academics to the people using it to make decisions for farming and ranching operations (Maunder, 1972). Contrariwise, problems and challenges in production agriculture require a mechanism to inform the research programs of land-grant scientists. Thus, agricultural extension systems also exist to effectively and efficiently identify community and stakeholder needs (Garst and McCawley, 2015), which plays a critical role in solving problems for production agriculture. In this chapter, I describe extension methodology and then use two recent livestock-specific extension projects as illustrations to explore the needs, target audiences, processes, and impacts of producing print and audio digital media content.

THE EXTENSION METHOD

Analogous to the scientific method, the 1st step of the extension method is to observe. In many cases, this reflects the identification of a problem or barrier by a stakeholder or extension professional (Ripley, 2011). Some problems may be resolved by providing existing information. However, if a problem is experienced widely throughout a region and no existing literature or resources presents a solution, then there is a sufficient need to develop new content or programming. Once a need has been identified, it is the responsibility of the extension professional to collect the relevant information. Personal experiences and previous encounters with similar problems may be useful

starting points, but empirical research and scientific evidence is ideal. If there is sufficient relevant information in the literature, the extension professional may need only to distill the information and synthesize it into a communicable piece of content. However, if there is a lack of relevant information in the literature, then the need extends beyond extension materials to research regarding the particular issue. In this way, producer questions help to inform the research programs of agricultural scientists under the land-grant system. Upon collection of adequate supporting information, the extension professional is prepared to begin creating a resource. The mode of delivery is often dictated by the nature of the problem being addressed. Chatterjee et al. (2018) categorized dissemination of extension materials into 3 broad areas: direct contact knowledge, indirect contact knowledge, and research publication / other creative activity-related knowledge. For relatively simplistic problems, indirect contact such as a note in a newsletter or a short bulletin may be sufficient. University of Nebraska- Lincoln Extension frequently publishes information in NebGuides, which are brief written overviews of specific topics. More complex topics may require direct contact by which information is delivered in-person via one-on-one producer consultations, classes, workshops, or presentations at symposia or conferences. Many extension professionals also make use of digital media content produced for a wide range of topics through instructional blogs, videos, podcasts, and webinars. The evolution of these tools has increased the reach and impact of programming in recent years. These modes of delivery would be considered part of the research publication / other creative activity-related knowledge area, along with peer-reviewed publications, needs assessments, and program evaluations. Collecting audience

feedback on prototypical materials helps to ensure that information is accessible and relevant to stakeholders (McCann and Stableford, 2015). It is common for extension programming to be accompanied by a survey of knowledge or skills gained. In some cases, pre- and post-tests are utilized to quantify improvements in ability resulting from the extension effort in order to improve existing content and allow for more streamlined development of future content. The following sections describe how the extension method was used to develop content for to different extension platforms.

ILLUSTRATIONS OF WRITTEN AND DIGITAL MEDIA APPROACHES TO EXTENSION

The NebGuide: Introduction to Animal Unit (AU) Concepts for Production of Small Ruminant Livestock

Collaborative conversations between University of Nebraska- Lincoln Extension and Nebraska Sheep & Goat Producers Association identified the need for small ruminant extension content to aid Nebraska sheep and goat producers. As of January 1, 2022, the state of Nebraska does not employ an Extension Educator or Extension Specialist with a small ruminant appointment, despite the state being home to over 80,000 sheep and lambs, 3,700 milk goats, and 20,000 meat goats and kids, per the National Agricultural Statistics Service. Extension professionals at South Dakota State University (**SDSU**) conducted a National Sheep and Goat Producer Needs Assessment in 2021. Of the 623 respondents from across the US, 50% had been raising sheep or goats for 10 years or less,

61% considered *Breeding Stock Nutrition* as Very Important, and 60% considered *Lamb and Kid Nutrition* as Very Important. Furthermore, 23% and 13% of respondents voluntarily noted *feeds/feedstuffs* and *grazing/pasture management*, respectively, as areas for improvement for their operations. The lack of Nebraska Extension sheep and goat resources combined with the nationwide demand for small ruminant nutritional and grazing information has created a need for extension programming in this area.

Since the SDSU 2021 Needs Assessment indicated that half of sheep and goat producers have less than 10 years of experience, initial extension materials should prioritize introducing fundamental concepts. One such concept is proper management and intentional utilization of grazing resources, which has the potential to improve animal productivity, range health, and soil regeneration (Russell and Bisinger, 2015). The lack of grazing management resources for small ruminant producers prompted the creation of a NebGuide introducing the Animal Unit (**AU**) system to help sheep and goat producers match forage demands of their animals with available forage resources. This guide also informs landowners of proper stocking rates for range and pastureland when leasing their grounds for grazing.

As illustrated in **Figure 3.1**, the process of creating this NebGuide started with the collection of relevant information from resources within and outside of the Nebraska Extension system. AU-related content for beef producers that was already present in the Nebraska Extension milieu included a report by Meyer et al. in the 2009 University of Nebraska-Lincoln Beef Cattle Report titled *Estimating Livestock Forage Demand:*

Defining the Animal Unit and a 25-minute webinar and brief guide by Wilke (2013) titled *Understand what an Animal Unit Month (AUM) is and its use in Range Management*. Animal unit equivalents (**AUE**) for classes of sheep and goats used for the NebGuide were based on information provided in the Nebraska Extension Circular titled *Grazing and Hay Records: Spreadsheet Template* (Volesky et al., 2008) with the help of Dr. Jerry Volesky (personal communication, November 2021).

Once the relevant information was identified and assembled, a draft document was prepared with the goals of 1) introducing technical concepts in non-scientific language to retain accessibility for lay audiences, 2) providing real-life examples to illustrate the application of the concepts, and 3) presenting calculations in a formulaic manner to allow producers to easily substitute their own values into the equations. A final draft was submitted for review to a panel of three Extension Specialists representing beef systems and forage agronomy expertise. After receiving their feedback, appropriate edits were made to the NebGuide. These included minor reformatting of example problems to increase clarity and the addition of a section about the diet selectivity of sheep and goats and how they differ from cattle. The final step in the process was submitting the NebGuide final draft and the accompanying figures and tables to the University of Nebraska Movement of Media portal for final editing, content formatting, and publication.

This NebGuide manuscript was submitted in January 2022 and is expected to be published in the coming months. The primary anticipated impact of this NebGuide is the

improvement of grazing management on range and pasturelands for sheep and goat producers. It will also raise awareness of these concepts for beef producers who may be considering adding sheep or goat enterprises to their operations. The Nebraska Extension Sheep and Goat webpage is currently housed on the Lincoln/Logan/McPherson County Extension website and does not contain any Nebraska Extension grazing resources for small ruminant producers. Expansion of such resources is not trivial, as the Nebraska Sheep & Goat Producers Association website estimates that there are 1,600 sheep and goat producers in the state of Nebraska, all of whom may benefit from the information in this NebGuide. It is worth noting that the Nebraska Extension Beef Systems unit reached over 659,000 stakeholders through the beef.unl.edu website, generated 127,000 viewers of *BeefWatch* YouTube videos, and recorded over 129,000 downloads of *BeefWatch* podcast episodes in 2021. Distribution of sheep and goat information through similar avenues will increase exposure and impact of these resources and raise interest in small ruminant production.

The Podcast: Nebraska Extension Digital Agriculture's *FarmBits*

The *FarmBits* podcast was launched by Nebraska Extension Digital Agriculture in the fall of 2020 with the objective of *exploring topics in digital agriculture in a well-rounded and accessible way, taking the shine off of new technologies through interviews with academic experts, farmers, and industry specialists.* In the fall of 2021, Nebraska Extension released a recruiting announcement for new co-hosts to the *FarmBits* production team to expand the podcast topics into new areas of expertise. Prior to this

announcement, *FarmBits* episodes were almost exclusively related to precision technologies in row crop production. This failed to represent animal agriculture topics, despite animal agriculture being a large proportion of Nebraska's economy (NASS, 2017).

Rapid development of digital tools for precision livestock farming will improve animal well-being by using data and metrics to, as Norton et al. (2019) noted, bring the producers *closer to the animals*. These tools are touted by agricultural media for their potential to improve decision-making power and increase profitability. Yet, ironically, there is reluctance among the agricultural media to adopt and utilize new technologies to promote agriculture and disseminate information outside of traditional means (Rhoades and Aue, 2010). Tools such as podcasts reach wider audiences and unique populations with different motivations than other forms of audio and digital media (Chan-Olmsted and Wang, 2022). Indeed, the on-demand, mobile nature of the podcast is particularly suited to the needs of farmers and ranchers. When SDSU Extension professionals surveyed sheep and goat producers about virtual/digital extension programming in 2021, the largest proportion of respondents (43%) desired a single-topic program up to 45 minutes in length. The *FarmBits* podcast is designed to be consistent with this model, with each episode focusing on a single topic and typically lasting 30 to 45 minutes.

The *FarmBits* podcast was created specifically to serve Nebraska agricultural producers interested in precision technologies despite often being applicable to agriculture in general. The addition of livestock topics has expanded the targeted audience to include Nebraska's 18,963 beef cattle producers, 250 dairy cattle producers,

1,346 pork producers, 1,660 sheep and goat producers, 1,553 horse breeders and trainers, and 519 producers of other animal species (NASS, 2017). As a co-host, my contribution to the *FarmBits* team has been to extend the reach of the show by addressing topics surrounding production and research in precision animal agriculture.

The *FarmBits* podcast follows the *Interview* format described by Tidal (2021). Co-hosts work in pairs to identify potential guests and invite them to participate in a recorded interview. Livestock-oriented episodes for the Fall 2021 season were intended to be introductory in nature, and episodes for the Spring 2022 season were included as part of the *Robotics & Automation* series. All interviews in which I co-hosted were conducted through Zoom to record both audio and video footage. Each guest was provided a list of potential questions developed by the co-hosts before the interview to allow them an appropriate amount of time to consider and prepare their responses. Following the recording of each interview, episodes were produced by the co-hosts using the Adobe Audition audio processor, as described by Cohen (2021). Post-production included the addition of *intro* and *outro* caps, theme music, and the removal of extraneous commentary. Video editing was conducted by the team media specialist using Adobe Premiere Pro. Episodes were distributed to streaming services through UNL's MediaHub and through YouTube for video versions only.

FarmBits episodes in my portfolio are detailed in **Table 3.1**. As of April 5, 2022, these episodes averaged 0.81 views/day, which is equal to one new view every 1.2 days. The benefits of online accessibility are illustrated by **Figure 3.2**, which demonstrates that earlier episodes of *FarmBits* continued to receive views well after their initial publication

date. *FarmBits* episodes are easily discoverable on YouTube and other platforms and may be shared independently by viewers with peers via instantaneous one-button links on various social media outlets as well as by word-of-mouth (Tidal, 2021). Comprehensive analytics from UNL MediaHub distribution were not available at the time of writing, but they are anticipated to surpass the level of engagement on YouTube. Edison Research reports in *The Infinity Dial 2021* that approximately 80 million Americans listen to at least one podcast weekly and that audience use of podcast media continues to grow meteorically. Nebraska Extension's 2021 Beef Industry Unit impact statement reported that their *BeefWatch* program had 129,000 podcast episode downloads and an additional 127,000 YouTube views in 2021 alone. Indeed, podcasts and other audio/video digital media are effective modes of communicating extension content with farmers and ranchers (Chivers et al., 2021), especially as in-person attendance at traditional meetings and workshops is increasingly limited by factors such as daily work obligations and COVID restrictions.

FUTURE DIRECTIONS

The evolution of new digital media forms (e.g., podcasts, video streaming services, social networking sites) continues to supplant traditional media services such as newspapers and commercial television and radio programs (Chan-Olmsted and Wang, 2022). Consequently, developing extension programming that takes advantage of stakeholders' increasing use of these digital tools is now necessary to rapidly and effectively convey information to improve animal welfare, productivity, and in turn

profitability (Norton et al., 2019). Nebraska Extension Digital Agriculture's *FarmBits* podcast and online publishing of NebGuides are examples of less-traditional mechanisms to provide essential service to the state via free, high-quality informational programming. Moreover, Nebraska Extension's continued expansion of scope to include NebGuides aimed at sheep and goat producers and *FarmBits* topics beyond row-cropping broadens its audience among Nebraska's animal agriculturalists and enhances interest and utility for years to come.

Figure 3.1 The process of creating a NebGuide.

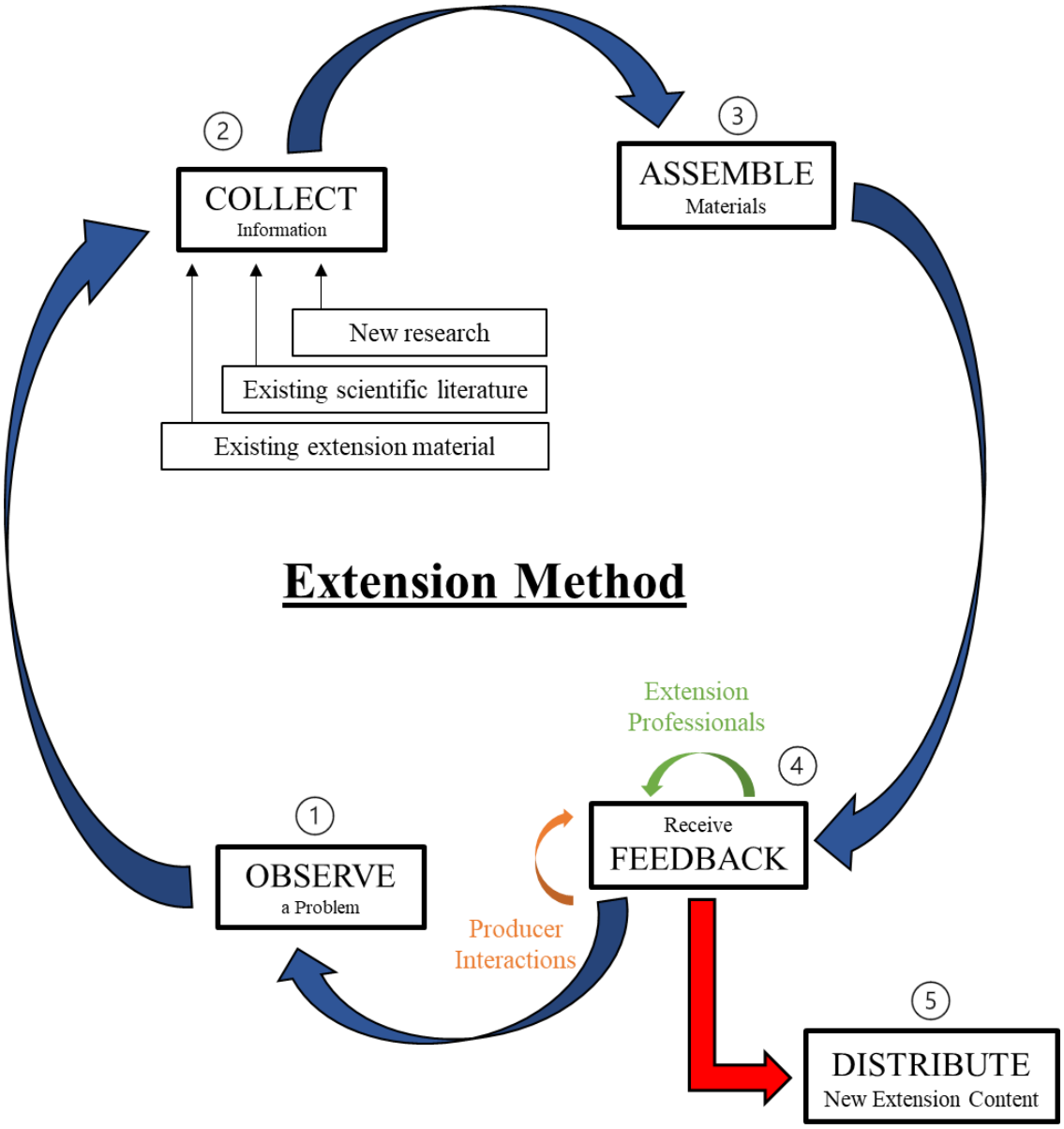

Figure 3.2 All-time *FarmBits* episode YouTube views.

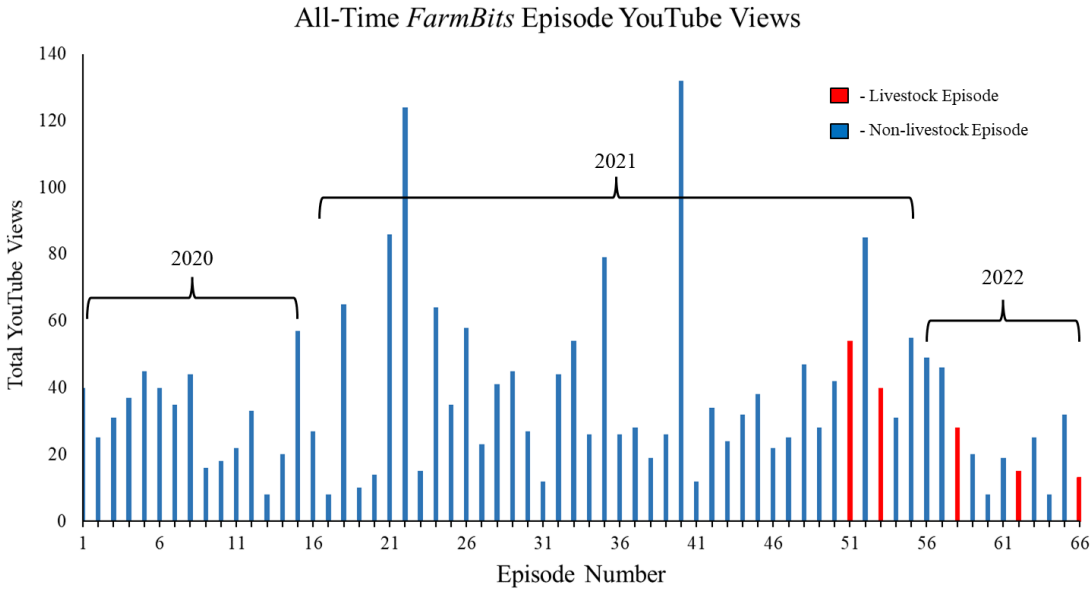

Table 3.1 Livestock-topic *FarmBits* episodes.

Episode #	Topic	Guest	Release Date	Total YT[1] Views	Days from Release to April 5, 2022	Mean YT Views/Day
50	Intro to Precision Animal Agriculture	Tami Brown-Brandl	28 October 2021	42	159	0.26
53	NUtrack Animal Behavior	Ty Schmidt & Haley Beer	18 November 2021	40	138	0.28
58	Precision Livestock Monitoring	Yijie Xiong, Jean Niwenshuti, Joshua Dotto	3 February 2022	28	61	0.46
62	Robotics in Dairy Systems	Jessi Sayers	3 March 2022	15	33	0.45
66	The Stock Cropper	Zack Smith	31 March 2022	13	5	2.60

[1]YouTube

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