Inflammatory Responses to Sub-Acute Ruminal Acidosis

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Introduction

Sub-acute ruminal acidosis (**SARA**) can occur as a consequence of feeding high energy rations to dairy cattle. During SARA, the rate of rumen short-chain fatty acid (**SCFA**) production exceeds SCFA absorption and results in an unhealthy depression of rumen pH. Definitions of SARA, derived primarily from experiments using ruminally cannulated animals, vary somewhat but typically require rumen pH to be below a certain threshold (5.5, 5.6, or 5.8) for a certain duration of time (Krause and Oetzel, 2006; Oetzel, 2007; Radostits et al., 2007). Zebeli and Metzler-Zebeli (2012) recently proposed that SARA be defined as rumen pH below 5.8 for 6 or more hours per day based on meta-analyses indicating that this threshold resulted in both a decrease in fiber digestibility and an increase in plasma levels of acute phase proteins.

At the level of the rumen, causes of SARA can broadly be classified as management, environmental, and animal factors, which reduce ruminal buffering capacity or increase ruminal SCFA accumulation. As reviewed by Stone (2004), buffering capacity can be increased by increasing dietary forage content and optimizing particle size to increase chewing and saliva flow, by addition of external buffers or alkalinizing agents to the ration, and by increasing the dietary cation anion difference of the ration. Buffering capacity can be reduced in response to heat stress or as a result of decreased chewing, for example due to feed sorting. The rate of SCFA production and the risk for SARA can be increased in response to increased dietary proportion of grain, increased fermentability of grains or forages, increased feed intake, and management factors that lead to larger and less frequent meals. It has also been proposed that cows might be at greatest risk for SARA immediately postpartum due to diminished size and absorptive capacity of rumen papillae following feeding of lower energy density diets during the dry period (Stone, 2004). However, Penner et al. (2007) were unable to reduce postpartum SARA by increasing concentrate feeding prepartum.

Consequences of SARA include feed intake depression, fluctuations in feed intake, reduced diet digestibility, reduced milk yield, reduced milk fat percent, gastrointestinal damage, liver abscesses, and lameness (Krause and Oetzel, 2006; Radostits et al., 2007; Plaizier et al., 2008). Injury to the gastrointestinal lining followed by localized or systemic inflammation appears to mediate many of these negative effects.

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Sub-Acute Ruminal Acidosis Effects on the Rumen and Hindgut

During SARA, ruminal accumulation of SCFA reduces rumen pH and causes a shift in rumen microflora (Zebeli and Metzler-Zebeli, 2012). Fiber and total carbohydrate digestion are reduced as a consequence of this shift, resulting in a loss of energy, and reduced body condition is sometimes noted without a concurrent reduction in intake (Hall, 2002; Kleen et al., 2003; Dijkstra et al., 2012). Khafipour et al. (2009b) evaluated changes in rumen fluid bacterial populations following experimental SARA challenges. Of the changes in bacterial population following a SARA challenge with wheat-barley pellets, the increase in *Escherichia coli* was positively associated with the severity of SARA symptoms, leading them to conclude that increases in *E. coli* may be important to the etiology of SARA. In another study, Mohammed et al. (2012) evaluated the population structures of rumen fluid bacteria both pre- and postpartum and associated those with the severity of SARA. They found that the magnitude of the population shift between prepartum and postpartum was independent of SARA susceptibility. Finally, Chen et al. (2011) found that the structure of the bacterial community adhered to the rumen epithelium changed when beef heifers were switched from a predominantly grass hay diet to a predominantly barley grain diet. Of interest, *Treponema*, *Ruminobacter*, and *Lachnospiraceae* species were found during high grain feeding. Shifts in rumen bacterial communities in response to SARA are believed to be a key first step in the negative impacts of SARA on animal performance.

Concurrent with shifts in microbial populations, there is also an increase in rumen concentrations of potentially toxic and inflammatory compounds during SARA. One that has received the most attention is endotoxin or lipopolysaccharide (**LPS**). The LPS is a component of gram negative bacterial cell walls, and presence of LPS within the body elicits an inflammatory response by mammalian cells. When animals are challenged with a SARA-inducing ration, the availability of fermentable carbohydrates initially results in logarithmic growth of bacteria, which is later followed by massive bacterial lysis in response to reduced availability of substrates, reduced rumen pH, and accumulation of fermentation end products (Zebeli and Metzler-Zebeli, 2012). Free LPS accumulates both during rapid growth and during bacterial lysis, resulting in increased rumen concentrations of LPS during SARA (Li et al., 2012). During an acute acidosis challenge in cows, rumen fluid collected following the challenge had increased endotoxin activity and became increasingly toxic when injected into mice (Nagaraja et al., 1978). These results led the authors to conclude that the effects of acidosis were mediated by systemic effects of rumen endotoxin. In addition, rumen concentrations of LPS were found to be negatively correlated with milk fat percentage and yield when cows were fed increasing levels of barley grain (Zebeli and Ametaj, 2009). Although rumen accumulation of LPS during SARA may be important for subsequent inflammatory responses, the immunoreactive properties of LPS differ among bacterial species. Khafipour et al. (2009b) propose that although rumen LPS increases in both grain-induced SARA and alfalfa pellet-induced SARA, inflammation is observed only in response to grain-induced SARA due to an increase in *E. coli* LPS. Other potentially harmful compounds produced during SARA include biogenic amines and ethanol (Ametaj et al., 2010). Ethanolamine is a biogenic amine that not only has potentially

harmful effects on the host but has also been shown to enhance growth and virulence factor production by pathogenic bacteria (Saleem et al., 2012; Zebeli and Metzler-Zebeli, 2012). Histamine is another biogenic amine produced during SARA and its potential role during the inflammatory response to SARA will be discussed in more detail later in this review.

The rumen epithelium serves as a selective barrier, allowing for absorption of SCFA while preventing entry and colonization by bacteria. Systemic effects of SARA are dependent upon a breach in this barrier. Structurally the rumen epithelium consists of four layers, the stratum corneum, stratum granulosum, stratum spinosum, and stratum basale (Figure 1). In the healthy rumen, bacteria are loosely associated only with the stratum corneum. Tight junction proteins that regulate the permeability barrier are expressed most heavily in the stratum granulosum and to some extent in the stratum spinosum (Graham and Simmons, 2005). Connections among the stratum granulosum, stratum spinosum, and stratum basale allow for the transport of SCFA from the rumen contents to the basal lamina (Graham and Simmons, 2005). The permeability barrier function of the rumen responds to changes in the animal or the rumen. For example, permeability is increased during oxidative stress or heat stress (Mani et al., 2012). Increased permeability may also be an adaptive response to higher grain diets to allow for increased uptake of SCFA (Zebeli and Metzler-Zebeli, 2012). Studies using isolated sections of rumen have also demonstrated increased permeability in response to acidification or hyperosmolality (Aschenbach and Gabel, 2000; Schweigel et al., 2005; Emmanuel et al., 2007; Penner et al., 2010).

In addition to its role as a selective barrier, the rumen epithelium helps direct immune function through its interactions with mucosa-associated lymphoid tissue (**MALT**). These microstructures are found throughout the digestive mucosa and consist of clusters of white blood cells including innate lymphoid cells and mast cells (Pearson et al., 2012; Kurashima et al., 2013). In a healthy animal, commensal bacteria are bound to mucous lining the mucosa instead of directly to the mucosa, and epithelial cells are able to communicate the composition of the microflora to MALT cells through various receptors such as toll-like receptor pathways (Taschuk and Griebel, 2012). Mucosa-associated lymphoid tissue cells respond to this signaling by regulating their production of cytokines that then activate or suppress other immune cells. During homeostasis, MALT cells are usually hyporesponsive, and proteins and enzymes produced by these cells help to maintain tight barrier function and regulate epithelial cell growth and differentiation (Mani et al., 2012; Kurashima et al., 2013). In response to a challenge, MALT cell signaling can induce a variety of responses including production of bactericidal proteases and antimicrobial peptides, recruitment of neutrophils, promotion of B cell differentiation to IgA producing plasma cells, and activation of T cells (Pearson et al., 2012; Kurashima et al., 2013). Signaling by MALT cells is also important for regulating division and differentiation of mucosal epithelium to allow for tissue repair. Altered communication between epithelial cells and MALT cells, as well as increased MALT cell activation are associated with gut inflammatory disease in animals and humans (Kurashima et al., 2013).

Downstream inflammatory effects of SARA are dependent on a breach in the permeability barrier of the rumen wall, causing Oetzel (2007) to conclude that rumenitis (inflammation of the rumen wall) is the fundamental lesion of SARA. During SARA, some combination of increased osmolality, reduced pH, increased bacterial toxins such as LPS, and increased biogenic amines leads to rumenitis. A study using isolated rumen and colon tissue from steers demonstrated that LPS and decreased pH acted synergistically to disrupt epithelial barrier function (Emmanuel et al., 2007). Once the epithelium has been breached, MALT cells respond by triggering local inflammation and altering cytokine production; this in turn further increases permeability and allows for colonization of papillae and increased entry of bacteria and toxins into the papillae which can enhance the inflammatory response (Mani et al., 2012; Kurashima et al., 2013). When cows were switched from a 0% grain ration to a 65% grain ration, the rumen epithelium underwent dramatic changes including visible papillae lesions, decreased tight junctions, sloughing of the stratum corneum, and presence of bacteria in the stratum granulosum and stratum spinosum (Steele et al., 2011). Khafipour et al. (2011) found increased RNA levels of virulence and adhesion factors in *E. coli* isolated during grain-induced SARA, indicating that SARA may increase the potential for pathogenic organisms to take advantage of a breach in epithelial integrity and colonize papillae.

Concurrent with local inflammation in the papillae are changes in epithelial cell cycle, adhesion protein expression, and SCFA absorption. We recently evaluated the transcriptome of rumen papillae 30 h following a SARA challenge and found 172 genes that were differently expressed (Mackey, 2013). Of those genes, one pathway that was unregulated by SARA was homophilic cell adhesion through increased expression of four protocadherin beta genes (Figure 2). Others evaluating rumen tissue from cows fed high forage or high concentrate diets have found dramatic differences in gene expression, including differences in genes for adhesion proteins and cell cycle regulation (Taniguchi et al., 2010; Steele et al., 2011). Injury to the rumen epithelium and changes to the cell cycle in response to SARA can result in parakeratosis or hyperkeratosis (Penner et al., 2011). Increased exposure of the lower epithelial layers to bacteria and toxins as a result of parakeratosis can further increase rumenitis and lead to the formation of microabscesses (Kleen et al., 2003). Both parakeratosis and hyperkeratosis can reduce SCFA absorption which may explain why SARA can become increasingly severe with repeated challenges (Dohme et al., 2008; Plaizier et al., 2008). Reduced rumen motility as a consequence of SARA can also decrease SCFA absorption. Differences in SARA absorption also impact SARA susceptibility, and those animals with greater rates of SCFA absorption are more resistant to a SARA challenge (Penner et al., 2009).

Events that occur in the rumen during SARA are mirrored in the large intestine. An increase in intestinal carbohydrate fermentation typically occurs concurrent with SARA and leads to increased concentrations of SCFA and LPS, a reduction in pH, and damage to the intestinal mucosa (Bissell, 2002; Dijkstra et al., 2012; Li et al., 2012). Fecal indicators of SARA include diarrhea, frothy feces, increased particle size in feces, and presence of mucin casts in feces (Hall, 2002). Because the intestinal epithelium is

composed of only a single layer of epithelial cells, it has been proposed that systemic inflammatory effects of SARA might be due to passage of bacteria or toxins through the intestinal mucosa (Oetzel, 2003). In fact, Khafipour et al. (2009a) found that the timing of the presence of LPS in the blood following a SARA challenge suggested LPS entered the circulation via the intestines instead of the rumen.

Systemic Effects of Sub-acute Ruminal Acidosis

If bacteria or toxins escape from the mucosa, they will typically be delivered to the liver via the portal blood supply. If live bacteria that manage to exit or bypass the liver, they can cause chronic inflammatory diseases in response to SARA such as pneumonia, endocarditis, pyelonephritis, and arthritis (Oetzel, 2007). Bacteria can also colonize the liver and form abscesses. *Fusobacterium necrophorum* is the primary agent isolated from liver abscesses in feedlot cattle, and the liver infection is secondary to infection of the rumen wall (Nagaraja and Chengappa, 1998). This normal inhabitant of the rumen increases in number in response to high grain diets and can opportunistically colonize a rumen wall that has been damaged by parakeratosis or rumenitis in response to SARA (Tadepalli et al., 2009). Bacterial products and toxins entering the liver can affect liver function as well. Haubro Andersen et al. (1994) found that during acute acidosis endotoxin was found in portal and hepatic veins even though it was not detected in the systemic circulation. Increased toxin flow to the liver can result in damage, and Bobe et al. (2004) noted that SARA can increase the likelihood of fatty liver which can further impair liver function.

One clear response of the liver to grain-induced SARA is production of acute phase proteins that can modify immune function and generate a systemic inflammatory response. The main bovine acute phase proteins are serum amyloid A, haptoglobin, LPS-binding protein, and α-1 acid glycoprotein, and they function to stimulate tissue repair, remove harmful compounds, isolate infectious agents, and prevent further damage (Zebeli and Metzler-Zebeli, 2012). Plaizier et al. (2008) summarized results from multiple SARA challenge studies and proposed that LPS, inflammatory amines, or other products of bacteria that reach the liver stimulate release of acute phase proteins from the liver and generate a systemic inflammatory response. Thus, systemic inflammation does not appear to be dependent on bacterial compounds reaching the general circulation. In addition to their release by the liver, mRNA expression of acute phase proteins has also been detected in the gastric mucosa, indicating that the mucosa may contribute directly to this inflammatory response as well (Dilda et al., 2012).

Studies have also been aimed at evaluating why grain-based SARA challenges induce an increase in circulating acute phase proteins while alfalfa-based SARA challenges fail to do so. In a study using cows with ruminal and cecal cannulas, Li et al. (2012) found that although rumen concentrations of LPS increased in response to both types of challenges, cecal concentrations of LPS only increased in response to the grain-based challenge. They propose that translocation of LPS from the large intestine to the liver of grain-challenged animals might account for the increase in acute phase

proteins. However, using challenge models that bypassed the rumen, we and others have been unable to generate similar increases in plasma acute phase proteins as found in response to high grain diets, perhaps due to the short-term nature of those challenges (Bissell, 2002; Mainardi et al., 2011). Khafipour et al. (2009b) found that of the microbiome shifts in response to SARA, rumen *E. coli* abundance, which increased only in response to grain-based SARA challenges, was most strongly associated with concentration of acute phase proteins in the blood. These results suggest that differences in bacterial products reaching the liver in response to dietary changes can differentially impact acute phase protein production. Khafipour et al. (2009a) also suggested that increased LPS binding protein concentrations in the blood are a direct indicator of LPS translocation from the rumen to the liver. As data on acute phase protein response to SARA continues to mount, it is becoming clear that direct passage of LPS or other bacterial products to the general circulation may not be necessary for the systemic inflammatory response to SARA. Instead, immune modulation at the level of the liver or even the gut mucosa seems to be sufficient to drive systemic inflammation.

Laminitis and lameness are consequences of SARA and it is likely that similar mechanisms to those driving systemic inflammatory responses to SARA also mediate hoof damage. In response to rumen acidosis, vasoactive substances including LPS and biogenic amines can be absorbed across the gut mucosa. Damage to the gut wall and entry of bacterial products can drive formation of endogenous vasoactive products including cytokines and prostaglandins. The primary effect of these exogenous and endogenous compounds is dilation of arterioles and constriction of venules which at the level of the gut can enhance inflammation and increase entry of toxins (Shearer, 2011). In the corium of the hoof, these vascular changes result in inflammation, hemorrhage, death of cells, activation of matrix metalloproteinases, and disruption of growth factor signaling (Shearer, 2011). Altered cell growth, cell damage, reduced oxygen and nutrient flow, and reduction of intercellular adhesion can cause sinkage of the pedal bone, damage to the corium, pain, and lesions (Nocek, 1997; Goff, 2006). Histamine that is absorbed from the gut or produced endogenously during inflammation has been proposed to play a key role in development of laminitis. In a study using bulls, Takahashi and Young (1981) demonstrated that grain overload and histamine injection to the digital artery acted synergistically to induce laminitis. As reviewed by Katz and Bailey (2012), equine laminitis resulting from starch overload occurs via a similar mechanism to that proposed in ruminants. A loss of barrier function in the gut allows for influx of bacterial products including LPS and amines into the portal circulation. The resulting inflammatory changes in liver and leukocytes, with or without systemic entry of toxins, is proposed to cause laminitis through vascular changes in the hoof, apoptosis, oxidative injury, and enzymatic degradation of the basement membrane (Katz and Bailey, 2012).

Conclusions

Sub-acute ruminal acidosis impairs cow performance and health. Rumenitis is the initial insult of SARA and results in inflammatory and immune activation which

reduces energy available to support production, allows for transfer of bacterial products across the gut epithelium, and can damage tissues including the liver and hoof. Risks of SARA can be reduced by following feeding recommendations including maintaining adequate particle size and physically effective fiber and avoiding excesses of fermentable carbohydrates (Stone, 2004). In their meta-analysis, Zebeli et al. (2012) additionally concluded that rations should contain at least 39% NDF and no more than 44% concentrate to reduce the risk of systemic inflammation; however they caution that their conclusions were derived from diets based on barley and wheat grain and thresholds might change for more slowly fermented corn-based rations. Although SARA is difficult to diagnose directly, feces can be monitored for signs of SARA (Hall, 2002). Inclusion of feed supplements such as linseed oil or fish oil that contain high levels of omega-3 fatty acids may help to reduce the inflammatory response and tissue damage that can result from feeding high carbohydrate diets (Mani et al., 2012). Other dietary supplements such as biotin and zinc have the potential to strengthen epithelium to prevent tissue injury from SARA (Goff, 2006). Finally, as we continue to increase our understanding of pathologic bacteria that contribute to SARA-induced tissue damage, there may be potential to develop management strategies to reduce the competitive ability of those organisms. For example, Gill et al. (2000) found that vaccination against *Streptococcus bovis* reduced the severity of response to an acute acidosis challenge in sheep, and future development of vaccines against pathologic bacteria associated with SARA might be beneficial. Sub-acute ruminal acidosis will likely continue to be a problem for the dairy industry as high energy diets are required to support high levels of milk production. Careful attention to nutritional management and development of new SARA mitigation strategies may help to reduce its impact in the future.

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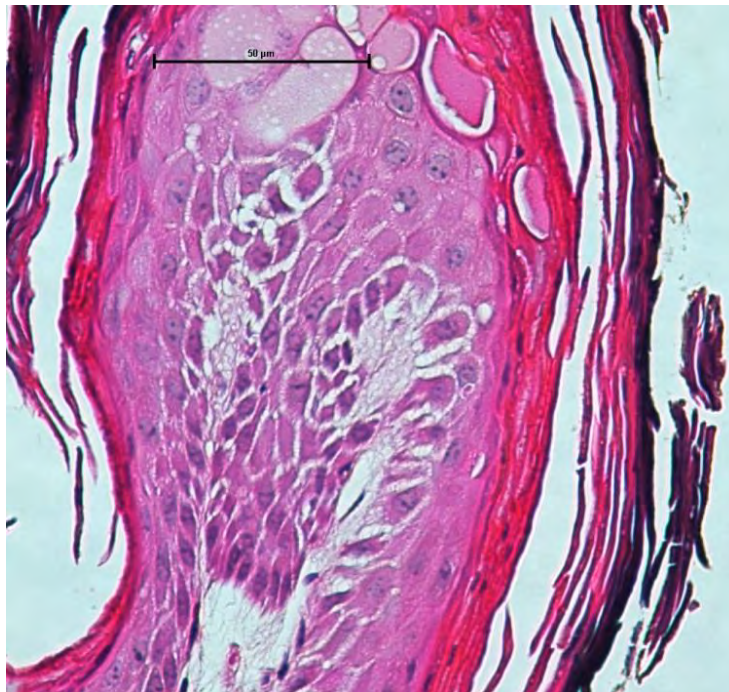
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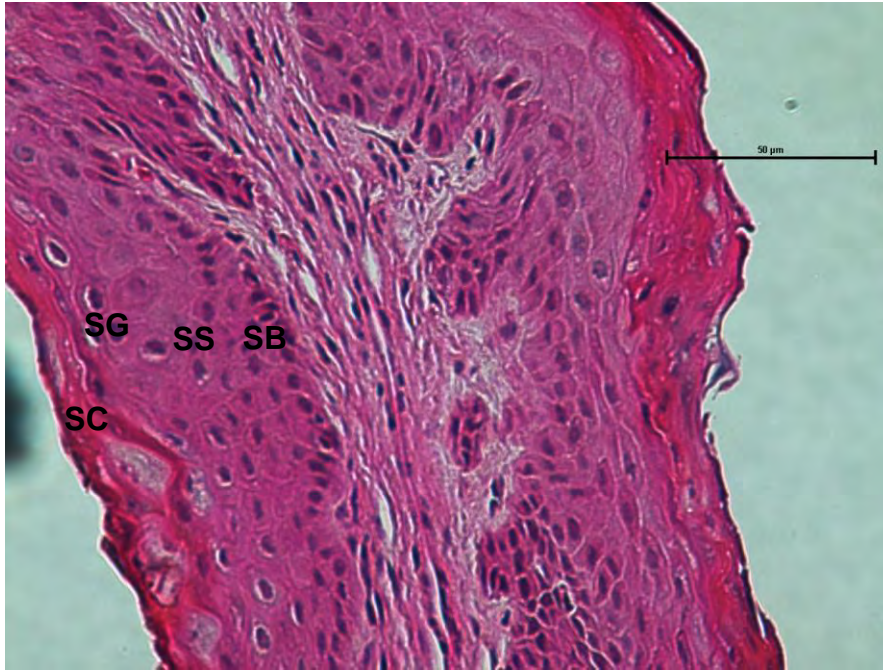
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Figure 1. A. Cross-section of a rumen papilla showing the stratum corneum (SC), stratum granulosum (SG), stratum spinosum (SS), and stratum basale (SB). **B.** Damaged papilla showing separation of stratum corneum.
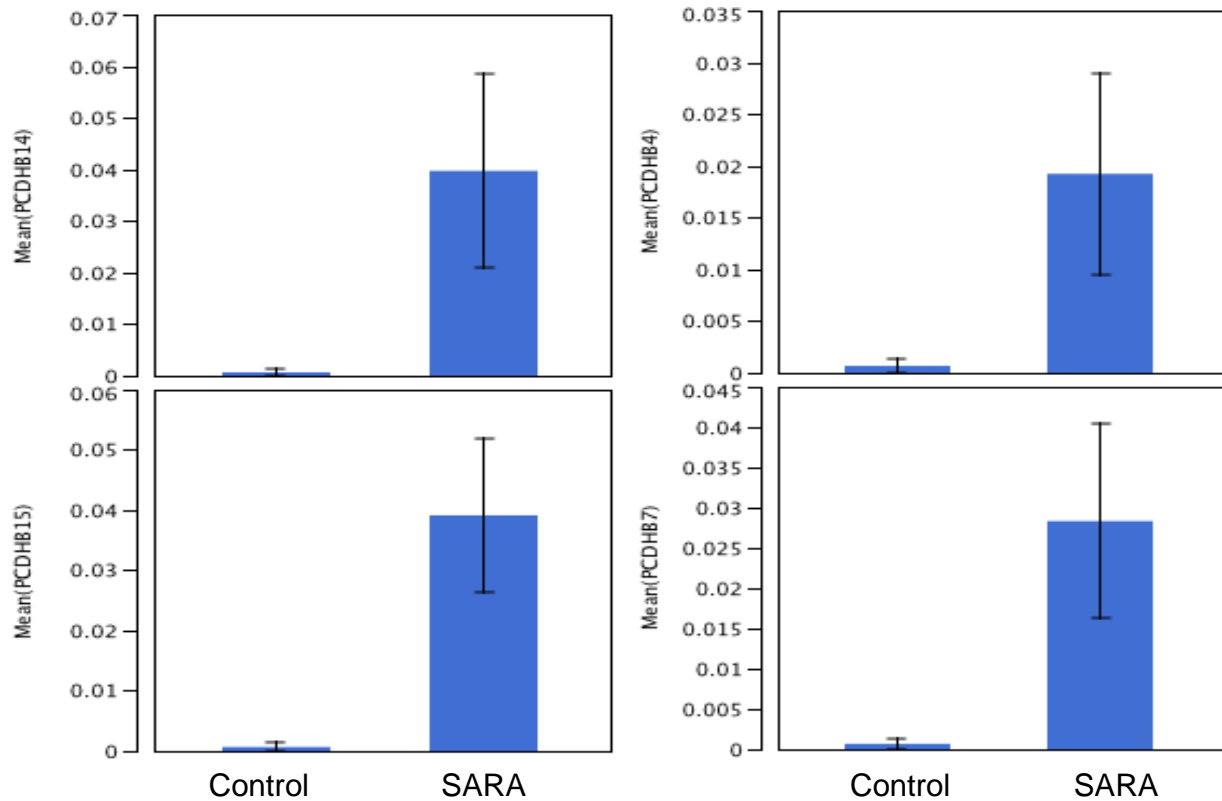
Figure 2. Expression levels of protocadherin beta (PCDHB) genes 4, 7, 14, and 15 at 30 hours following a SARA challenge. These homophilic cell adhesion genes (PCDHB14: top left, PCDHB15: bottom left, PCDHB4: top right, and PCDHB7: bottom right) were greater in SARA-challenged cows (right bars) than control cows (left bars).

SESSION NOTES