

Large Animal VETERINARY Rounds™

NOVEMBER 2005
Volume 5, Issue 9

AS PRESENTED IN THE ROUNDS OF THE DEPARTMENT OF LARGE ANIMAL CLINICAL SCIENCES
OF THE WESTERN COLLEGE OF VETERINARY MEDICINE, UNIVERSITY OF SASKATCHEWAN

Advances in pathophysiology of equine laminitis: Are there lessons to be learned from organ failure in human sepsis?

By Jim Belknap DVM, PhD, DACVS

To date, most of the intellectual energy of the critical care community has focused on optimization of tissue oxygenation to avoid ischemic cell damage... Despite billions of dollars invested, no specific drug or therapy has been developed to effectively prevent the onset of SIRS (systemic inflammatory response syndrome) or MODS (multiple organ dysfunction syndrome).¹

This quote is from a recent review article about organ failure in human sepsis patients, which discusses recent evidence indicating that it is not organ ischemia, but direct cellular damage (mainly from inflammatory events) that leads to organ failure.¹ However, this quote could easily be transposed to the treatment of equine laminitis, where decades of work on ways to address a hypothesized laminar ischemia have led to minimal success in treating the disease process. The clinical picture for equine subjects with diseases placing them at risk of laminitis is strikingly similar to human sepsis patients at risk of organ failure. Equine cases with colitis, post-colon torsion, or post-grain overload usually exhibit comparable clinical characteristics to those defined for SIRS in early human sepsis. Our laboratory at Ohio State University and others have taken advantage of these similarities to explore new areas of investigation in laminitis. This issue of *Large Animal Veterinary Rounds* uses some of the newer data, mainly from models of laminitis using black walnut extract (BWE) or carbohydrate overload, to discuss the role that bacterial toxins, inflammation, digital hemodynamics, platelet activation/thrombosis, and matrix metalloprotease (MMP) activation may play in the pathophysiology of laminitis. Many analogies to human sepsis-related organ damage are evident.

Models of laminitis

Models of laminitis used in the studies described below include those administering BWE, in which a developmental period – defined by the onset of leukopenia – occurs approximately 3 hours after administration. Approximately 10-12 hours afterwards, clinical signs of lameness begin to occur. In carbohydrate-overload models (including starch and oligofructose), a developmental period characterized by a drop in central venous pressure occurs approximately 12 hours post-carbohydrate administration. The majority of the research, however, has been performed at the onset of clinical signs, which occurs approximately 40 hours following carbohydrate administration. It is important to realize that many of the deleterious laminar changes noted below occur in the developmental periods and thus occur when there are no clinical signs of laminitis.



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The Canadian Veterinary Medical Association recognizes the educational value of this publication and provides support to the WCVM for its distribution.

Bacterial toxins in laminitis

The controversy regarding the role that either Gram-negative or Gram-positive toxins play in laminitis has not been resolved; however, as discussed below, it is likely that, similar to human sepsis, both may play a role in the disease process placing a horse at risk of laminitis.

Endotoxemia, commonly associated with systemic inflammation in humans and animals, appears to be a prominent feature of many of the disease processes that put a horse at risk of laminitis; these include abdominal crises (eg, colitis, grain-overload cases, and ischemic lesions of the large and small bowel), and Gram-negative infections seen in some pleuropneumonia and acute metritis cases.² These animals commonly exhibit many of the symptoms described for SIRS that are observed in humans with sepsis, including tachycardia, leukopenia, fever, and mucous membrane changes. Despite overwhelming clinical evidence of endotoxemia-like signs in the majority of animals at risk of laminitis, the role of endotoxemia in the laminitic process has been controversial because numerous investigators have been unable to detect systemic endotoxin in laminitis models³ and endotoxin administration does not induce laminitis or the same digital hemodynamic changes observed in laminitis models.⁴

The apparent discrepancy between clinical experience and laboratory results may have been resolved in a paper addressing grain overload in cattle, in which the investigators could detect endotoxin in portal blood, but not in systemic blood.⁵ Thus, endotoxemia may be present in the early stages of laminitis, but most of the endotoxin may be rapidly cleared by organs such as the liver and lungs, limiting the detection of endotoxin in the systemic circulation. There has also been recent work on the role of exotoxins from Gram-positive streptococcal species (present in the hindgut of horses) in gastrointestinal diseases leading to laminitis.⁶ Although some investigators have interpreted these data to indicate that only Gram-positive toxins play an important role in the initiation of laminitis, they do not fit the clinical scenario, in which an animal with specific Gram-negative sepsis (eg, Gram-negative pleuropneumoniae or coliform mastitis in cattle) is at risk of laminitis. By examining human sepsis, where diseases associated with Gram-positive toxins, Gram-negative toxins, or a “cocktail” of Gram-positive and -negative toxins, can result in sepsis-related organ failure,⁷ a similar scenario could be expected in laminitis. This would be especially true in gastrointestinal disease, where a loss of the mucosal barrier leads to the absorption of a plethora of different bacterial toxins.

Inflammation

The presence of inflammation in the laminae has been a source of controversy in the past, mainly due to a lack of histologic evidence of inflammatory cells in the early stages of the disease process. This led to suggestions that the term “laminitis” should be changed to “laminar degeneration” in the 1990s. However, in the past 5 years, the use of modern molecular and biochemical research techniques has led to the documentation of a marked inflammatory process in the developmental stages and at the onset of the disease process. As with organ failure in human sepsis, leukocyte emigration into the laminae appears to play a significant role in early laminar inflammatory changes.

Inflammatory mediator expression

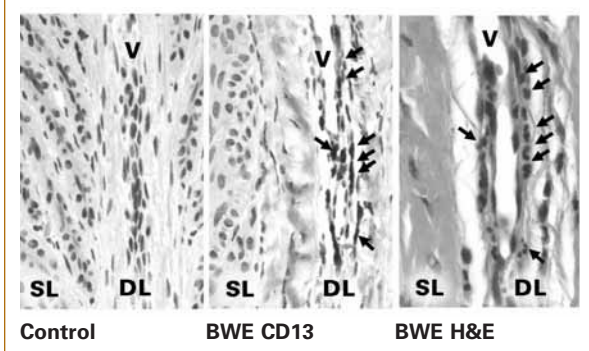
The first report indicating the occurrence of inflammatory processes in the early stages of laminitis was published in 2001. The authors found perivascular cells undergoing gene expression of the central proinflammatory cytokine, interleukin (IL)-1 β , in the dermal laminae of horses during the developmental stage of BWE-induced laminitis.⁸ More recently, a screening project at Ohio State University for genes that undergo differential regulation between normal laminae and laminae from the developmental stage of the BWE model focused attention back on the inflammatory cytokine signaling mechanisms. The first product our group isolated was the nuclear protein MAIL (Molecule with Ankyrin repeats Induced by Lipopolysaccharide, also known as I κ B-zeta). This protein is central to the induction of expression of another central proinflammatory cytokine, IL-6, when cells are stimulated by inflammatory mediators or bacterial toxins (eg, IL-1 β and lipopolysaccharide).⁹ In the same study, quantitative polymerase chain reaction (PCR) techniques were used to demonstrate marked increases in both IL-1 β (30-fold) and IL-6 (160-fold) at the same developmental time point.⁹

Our laboratory has recently assessed the laminar expression levels of cyclooxygenase (COX)-1 and the inducible COX-2 isoform in the prodromal/developmental stages and at the acute onset stage of laminitis in the same model. We found marked increases in COX-2 mRNA and protein concentrations in the developmental stage of the disease process.^{10,11} Similar to the trend for a peak in expression by some of the inflammatory cytokines during the developmental stage of laminitis, our recent data indicate that COX-2 protein concentrations also peak during this developmental stage, with a much lower magnitude of COX-2 induction at the onset of clinical signs for laminitis.¹²

Laminar leukocyte infiltration

Much of the inflammation and tissue damage leading to organ failure in human sepsis is initiated by emigration of

Figure 1: Leukocyte emigration into laminae¹³



Control: Note the lack of leukocytes (CD13⁺/Immunoperoxidase positive/brown cells) in the normal equine laminae.

BWE CD13: There are a large number of CD13⁺ cells (brown cells) in the primary dermal laminae (DL) around the laminar venules (V) in the black walnut extract (BWE)-treated animals.

BWE H&E: Note that in the higher magnification shot of a serially cut section exhibited to the right (BWE, H&E), the CD13-positive cells are neutrophils.

SL = secondary laminae.

neutrophils into organ tissues. We have used a histochemical marker for equine neutrophils and monocytes and have determined that, while leukocytes are not present in the normal laminae, there is a marked influx of neutrophils into the laminar interstitium in the BWE model of laminitis (Figure 1).¹³ We also found the same emigration of neutrophils out of the dermal vasculature in the skin of BWE-treated horses. Additionally, investigators at the University of Georgia have preliminary evidence of systemic activation of leukocytes at the same time point in the same model. Thus, it appears that laminar injury may have the same initiating factors that are observed for organ injury in human sepsis where activated leukocytes emigrate through a vascular lining (endothelium) that is inflamed by circulating toxins and/or cytokines. Neutrophils can induce many deleterious downstream effects due to the production of numerous mediators, including oxygen radicals, proinflammatory cytokines, and metalloproteases.

Regarding the question about why the laminae are commonly the sole “target organ” in the horse at risk of laminitis (vs. MODS in human sepsis), we recently found that there is minimal superoxide dismutase (SOD) activity in the equine laminae, in comparison to normal levels in other equine tissues. Since SOD is a key enzyme in protecting tissue from oxygen radical damage, the unique lack of this enzyme in the laminae may make the tissue particularly prone to damage by reactive oxygen species (ROS) released by emigrating neutrophils.

Hemodynamic events in laminitis

As was true 30 years ago, one of the major current controversies concerning the pathophysiology of laminitis is whether ischemia exists in the laminae in the

early stages of the disease. Interestingly, the same controversy regarding the dogma that ischemia is necessary for organ failure has plagued the pathophysiology of organ failure in human sepsis for years. However, in the past few years, researchers have proven that organ damage in sepsis is due more to cellular damage from inflammatory mediators, and that organ failure commonly exists with no tissue ischemia.

The majority of recent scientific data supporting ischemia as the primary mechanism in laminitis is based on studies of hemodynamics and Starling forces using the denervated, extracorporeally perfused, (disarticulated) digit in the anesthetized horse,¹⁴ and Doppler ultrasound studies to assess laminar blood flow in the standing horse.¹⁵ A general conclusion from these studies in support of ischemia is that a decrease in laminar blood flow occurs in the developmental stages of laminitis, most likely due to venoconstriction and possibly, capillary collapse from increased interstitial pressure.¹⁵ Conflicting reports have been obtained using hoof wall temperature as an indicator of laminar blood flow. One investigator reported decreased temperature (and therefore blood flow) in the prodromal stage,¹⁶ whereas another investigator reported increased hoof wall temperature.¹⁷

Due to the inability of the physiologic models to differentiate between arteriovenous (AV) shunting and changes in laminar microvascular perfusion, our laboratory recently used a molecular and protein biochemical approach to assess the expression/presence of mediators during ischemia or ischemia/reperfusion. The preliminary data indicate that the laminar pattern of gene expression of 7 hypoxia-related genes is not consistent with ischemia. However, because we have not determined a positive control for laminar ischemia and although these data do not support ischemia, they certainly do not disprove it. We also recently reported no increase in the conversion of xanthine dehydrogenase to xanthine oxidase in laminar tissue during the developmental stage of laminitis in the BWE model, a conversion that should take place if ischemia/reperfusion were present. Nevertheless, although the data are not supportive of ischemia, the high degree of variability in xanthine oxidase activity between horses does not allow us to dogmatically state that no global laminar ischemia exists in the early stages of laminitis.

There are other data that do not support ischemia as the primary mechanism in laminitis. For example, similar leukocyte emigration occurs in the skin and laminae in the early stages of laminitis.¹³ However, since ischemia is postulated to occur only in the digit, the same changes would not be expected to occur in the skin. When attempting to combine all of the data on digital hemodynamics in laminar failure and hemodynamic studies in sepsis-related organ failure, the likely explanation is that there are disturbances in vascular flow and, depending on the model or clinical ill-

ness (eg, hypovolemic shock), in some cases, these disturbances may be of an adequate severity to allow ischemia to play a role. However, we are finding strikingly similar patterns of pathophysiologic mechanisms in laminar failure and organ failure in human sepsis (including a consistent lack of drug efficacy in addressing ischemia). It is likely that ischemia will be determined to play a less important or less consistent role than the marked inflammatory processes now known to occur in the early stages of laminitis.

Altered digital blood flow due to thrombus formation

Thrombi have been identified in the vessels of laminitic digits of horses with both clinical and experimental laminitis.^{18,19} Radioisotope-labeled platelets have demonstrated localization of platelets and platelet-neutrophil complexes in the digital microvasculature of horses with laminitis.²⁰ Importantly, an inhibitor of platelet aggregation was effective in reducing the incidence of laminitis in an experimental model.²¹ Detracting from the importance of thrombus formation playing a central pathophysiologic role is the point, commonly raised, that thrombi/microthrombi cannot be found in all animals exhibiting signs of laminitis. It is also questionable whether the number of thrombi found could lead to global laminar ischemia.²⁰ However, since activation of platelets and coagulation are both now known to promote endothelial inflammation/activation and leukocyte adhesion and margination into organ tissues in human sepsis,²² platelets are likely to play a similar important role in the early stages of laminitis.³ The role of platelet activation/adhesion in exacerbating endothelial and tissue inflammation (possibly without producing occlusive thrombi) may account for the efficacy of platelet and coagulation inhibitors in reducing the incidence of laminitis in experimental models.

Breakdown of the basement membrane in the digital laminae

The breakdown of the basement membrane underlying the epidermal cells of the secondary epidermal laminae has recently been well-documented in laminitic digits using histologic and histochemical techniques.²³ This breakdown in the connective tissue binding the dermal and epidermal laminae is proposed to occur due to upregulation and activation of MMPs (eg, MMP-2 and MMP-9). MMP-9 activation has been noted in clinical cases of laminitis²⁴ and our lab has found the same MMP-9 activity in the early stages of BWE-induced laminitis. MMPs can be induced and/or activated by a host of factors likely to be present in laminitic laminae, including bacterial toxins, proinflammatory cytokines, and ROS. Thus, a great deal of data support an important role for MMPs in the laminar destruction occurring in laminitis. However, investiga-

tions regarding the efficacy of MMP inhibitors in reducing laminitis in the clinic are still needed to confirm the importance of these enzymes. There is a paucity of data on the clinical use of MMP inhibitors in the treatment of laminitis, although cryotherapy (eg, cold water foot baths) may reduce the activity of these enzymes.

Treatment based on the information above

Overall, recent data may open a new era in the treatment of laminitis because we now have a better understanding of the pathophysiologic mechanisms. We may be able to abandon less efficacious treatments and focus on some new target areas. Additionally, a close watch on drug research in human sepsis may, we hope, offer the opportunity to gain rapid ground in new treatment modalities, while avoiding the clinical failures evident from human clinical trials.

- Treatments aimed at neutralizing bacterial toxins, especially endotoxin, would appear to be indicated, yet the main treatment entities, endotoxin antiserum and polymyxin B, have had limited efficacy in controlled studies. Conflicting reports exist regarding the efficacy of endotoxin antiserum, with 2 reports of limited or no efficacy in models of equine endotoxemia.^{25,26} Polymyxin B, which has experimental support for treating endotoxemia,²⁶ was not effective in preventing experimental laminitis.

- The same dramatic increase of inflammatory cytokine expression observed in human sepsis has been demonstrated in laminitis; however, the consistent failure of cytokine blockage in the treatment of human sepsis most likely indicates that targeting individual cytokines will not be effective in laminitis. The most effective anti-inflammatory treatments may continue to be nonsteroidal anti-inflammatory drugs (NSAIDs). Despite the fact that pentoxifylline, a hemorrheologic agent used in laminitis, demonstrated anticytokine activity in experimental laboratory rodent endotoxemia/sepsis models, the drug did not decrease tumour necrosis factor (TNF) activity in an equine model of endotoxemia.²⁷ Further, since we have found marked laminar expression of COX-2 and other inflammatory mediators early in the pathogenesis of laminitis many hours prior to any clinical signs of laminitis, it is most likely beneficial to initiate aggressive NSAID treatment as soon as possible in horses at risk for laminitis. Since signs of laminitis do not commonly appear until 40-72 hours after the initiating insult; it is warranted to continue aggressive NSAID therapy for this period in horses at risk for the disease. The author uses full dose flunixin meglumine (1.1 mg/kg IV TID, with close attention to maintaining hydration status) in animals with diseases that place them at risk of laminitis. Another possible advantage to using higher concentra-

tions of NSAIDs is a blockade of other inflammatory cascades (eg, the potent cytokine inducer, NF- κ B), in addition to cyclooxygenase inhibition. Although COX-2 selective inhibitors may play an important role in the future, investigators need to ensure that the adverse vascular effects (eg, blood vessels more prone to thrombus formation) associated with the use of COX-2-selective inhibitors (rofecoxib and celecoxib) in humans, do not occur in the inflamed endothelium in acute laminitis.

- Our recent finding of leukocyte infiltration into the laminae, similar to that in organ failure in human sepsis, indicates that, just like human sepsis therapy, attention should be given to treatments decreasing leukocyte activation and oxidative damage in the laminae due to superoxide radicals released by activated leukocytes. The need for antioxidants/oxygen radical scavengers is further emphasized by the recent finding of minimal SOD activity in the laminae. The only treatment commonly available at this time with oxygen radical scavenging properties is intravenous (or oral) dimethyl sulfoxide (DMSO; usually administered at up to 1 g/kg in a 10%-20% solution). Although there is scientific evidence that DMSO is an effective radical scavenger,²⁸ negligible data are available in the horse (or in vivo in any species).

- One treatment reported to have some efficacy in decreasing leukocyte activation in other species is intravenous lidocaine. Thus, IV lidocaine, commonly given to horses for postoperative ileus, may be indicated for treating animals at risk of laminitis.

- Treatments to increase blood flow to the laminae have had minimal success in laminitic horses, with several therapies (eg, pentoxifylline, isoxsuprine, nitroglycerin paste) undergoing initial peaks in use, followed by clinical and experimental data indicating a lack of efficacy. The one “vasodilator” treatment used for decades in laminitis treatment and with some scientific evidence to indicate that it increases digital blood flow, is IV acepromazine. However, it was recently demonstrated that intramuscular acepromazine does not increase digital blood flow (preliminary data). The combination of the controversy regarding the presence of ischemia in laminitis and the limited efficacy of therapies for tissue ischemia in both human sepsis and laminitis indicates a need to change the focus of treatment, possibly towards some of the newer pathologic mechanisms discussed in this article.

- The reported efficacy of platelet aggregation inhibitors and the roles that coagulation and platelet activation/aggregation are known to play in sepsis-related organ damage may indicate that a renewed interest in these treatments is indicated for laminitis. Although heparin was demonstrated to decrease the incidence of laminitis when given prior to administra-

tion of a carbohydrate overload, conflicting reports exist regarding its efficacy in clinical laminitis cases. An additional concern is that unfractionated heparin induces red blood cell agglutination in horses. These agglutinated cells appear to lodge in capillaries, most likely including laminar capillaries, and may have deleterious side effects on inflamed laminar microcirculation. Low molecular weight heparin, which does not cause erythrocyte agglutination, may become a valuable therapy. Attention should be given to clinical trials of drugs targeting platelet aggregation/coagulation in human sepsis for potential future use in laminitis therapy (eg, the recent successes and failures with activated protein C).

- No specific MMP inhibitors have been tested in vivo in laminitis cases. However, human cancer research has recently resulted in the production of numerous MMP inhibitors (many are modified tetracyclines) and there is the potential for the future use of these drugs in laminitis. In current therapies, the only one that may decrease MMP activity is “cryotherapy,” as reintroduced by Pollitt, where the induction of tissue hypothermia by placing the distal limb in boots containing iced water may decrease enzyme activities (and overall metabolic rate).²⁹

Summary

Recent advances in the understanding of the pathogenesis of laminitis suggest a remarkable similarity between laminar failure in laminitis and organ failure in human sepsis, including a central role for inflammatory mediators in the development of laminitis. These recent discoveries should lead to novel therapies over the next few years, especially in the context of blocking leukocyte infiltration and decreasing oxidative damage to the laminae. Treatments in our current drug arsenal that are indicated by the latest research include:

- aggressive use of NSAIDs
- intravenous lidocaine to reduce leukocyte activation
- possibly, DMSO as a free radical scavenger to decrease oxidative damage.

Further clinical studies are indicated to assess the safety and efficacy of cryotherapy (ie, cold water foot baths) in the clinical equine case at risk or in the early stages of laminitis.

Jim Belknap, DVM, PhD, DACVS, is an Associate Professor of equine surgery at Ohio State University and active as a clinician and consultant on clinical cases of laminitis. Dr. Belknap has run a research laboratory for the past 9 years focused on the pathophysiologic mechanisms occurring in the early stages of laminitis. He has published over 50 papers and abstracts on the pathophysiology and treatment of laminitis.

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This publication is made possible by an educational grant from

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