

A Review of the Pathophysiology and Treatment of Acute Laminitis: Pathophysiologic and Therapeutic Implications of Endothelin-1

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The pathophysiology of acute laminitis remains poorly understood despite substantial scientific investigation over the last 20 yr. Evidence would suggest that ischemic and inflammatory cascades are involved. Evidence from our laboratory suggests that endothelin-1 is involved in the digital microvascular alterations characteristic of acute laminitis. Although current therapies are varied and inconsistent in their effectiveness, newer, novel, and more effective treatments can only be developed as we gain a better understanding of the pathophysiology of this devastating disease.

Based on information from our laboratory, further investigation into the potential therapeutic use of endothelin antagonists for the prevention and treatment of laminitis in horses is warranted. Authors' addresses: Equine Health Studies Program, Departments of Veterinary Clinical Sciences (Eades, Moore) and Comparative Biomedical Sciences (Holm, Moore), School of Veterinary Medicine, Louisiana State University, Baton Rouge, LA 70803. © 2002 AAEP.

1. Introduction

Acute laminitis (founder) is a severely debilitating, excruciatingly painful, and potentially career-ending and life-threatening disease of the soft tissues (sensitive and insensitive laminae) of the equine digit. Laminitis is important to all horse owners/trainers and horse enthusiasts because it can occur in adult horses and ponies of any breed or use (athletes or companions/pets). Laminitis usually occurs secondary to other diseases such as acute gastrointestinal tract disease (colic), particularly strangulating obstruction and inflammatory bowel disease (anterior enteritis and enterocolitis), grain overload, retained fetal membranes and subsequent metritis, pleuropneumonia, and other diseases accompanied by endotoxemia. Additionally, support

limb laminitis occurs commonly in the contralateral limb because of overload or excessive weight bearing in horses that have a severe non-weight bearing lameness (fractures, bone, or joint sepsis) in the opposite limb.

Laminitis is extremely frustrating for veterinarians because our current knowledge and understanding of the pathophysiology and progression of the disease is incomplete, limiting our ability to successfully prevent and treat this devastating disease. Laminitis causes profound emotional stress and economic loss to horse owners and trainers because of the agonizing pain experienced by these horses. This disease often leads to poor body condition and prolonged periods of recumbency with secondary pressure sores. Many of these horses will only rise

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for short periods of time and demonstrate a characteristic stance of rocking or shifting their weight onto their rear feet, which is accompanied by anxiety, muscle fasciculations, and sweating. Approximately 75% of laminitic horses treated at a university hospital did not return to athletic soundness; the majority of these horses were ultimately euthanized because of severe pain associated with separation of the sensitive and insensitive laminae resulting in rotation and/or distal displacement of the third phalanx.¹

It is estimated that 15% of horses in the United States are afflicted with laminitis over the course of their lifetime, and 75% of these horses develop severe or chronic lameness and debilitation that necessitates euthanasia. These represent a substantial number of horses in the United States and worldwide, which suffer from this devastating disease that are ultimately destroyed. From an economic perspective, the diagnosis and treatment of laminitis is estimated to cost approximately \$8 million annually, and the monetary loss of animals euthanized each year subsequent to complications of laminitis is approximately an additional \$5 million.

Scientific investigations have shed light on the pathophysiologic events involved with laminitis; however, additional studies are needed to unravel the remaining mysteries regarding the initiation and propagation of laminitis. Currently, numerous and varied therapies are employed in the prevention and treatment of laminitis; however, clinicians' preferences and impressions regarding the most effective treatments are based on an incomplete understanding of the initiating events in this disease. Because of the gaps in our knowledge of the pathophysiology of laminitis, the effectiveness of the currently employed treatments is inconsistent at best. Therefore, developing a more thorough understanding of the cascade of events involved with the onset and propagation of acute laminitis should help us to develop more rational, effective, and cost-efficient therapies for the prevention and treatment of a disease with profound humane, emotional, and economic effects on horses, horse owners/trainers, and veterinarians. The purpose of this paper is to provide a comprehensive review of the current knowledge of the pathophysiology of acute laminitis and to present experimental findings that should contribute to a better understanding of this pathogenic cascade and may potentially help to improve the prevention and treatment of laminitis in horses.

2. Anatomy and Physiology of the Digital Vasculature

The normal laminar tissue and its vasculature are unique in numerous aspects. The ability of the equine athlete to walk depends on the integrity of the interdigitations of the primary and secondary laminae, which provide a firm bond between the hoof wall and the laminar corium. This attachment of the corium (dermis) helps to maintain proper anatomic alignment with the distal phalanx.

The nutrients for maintenance of the integrity of the corium come from the laminar arteries branching from the circumflex artery as it curves around the toe.² These laminar arteries course in a distal to proximal direction. Metabolic wastes are removed by the laminar veins that course distally into the circumflex vein draining into the bulbar vein and digital veins.² Arteriovenous shunts between the circumflex artery and vein have been demonstrated in acute laminitis.² These shunts could alter hoof temperature by providing a path of rapid flow from the laminar arteries to the veins bypassing the laminar capillaries. However, this flow pattern robs the laminae of nutrient flow through its capillary bed.

The digital arteries and veins supplying the hoof have unique characteristics. The digital veins are highly muscular compared with veins in other tissues and other species.³ This muscular wall is probably needed to withstand the high vascular pressures exerted in these dependent tissues. The highly muscular wall is likely responsible for the low compliance of the veins.³ In exercising horses, the pressure in the venous circulation may reach 200 mm Hg.⁴ The equine digital arteries and veins are highly sensitive to vasoconstrictive substances, most notably norepinephrine and endothelin.⁵ Furthermore, the digital veins are most sensitive *in vitro* to vasoconstrictive substances.⁵ For example, contraction induced by angiotensin, thromboxane, norepinephrine, serotonin, and endothelin is twice as strong in veins as arteries. The culminating effects of low compliance and high sensitivity to vasoconstrictive substances predispose the equine digit to high venous pressures, thereby increasing hydrostatic pressure and thus the likelihood of edema formation.

The microcirculation of the equine foot is poorly adapted to handling edema. In normal tissues, there are three safety factors that counteract edema formation, including capillary permeability, pre-to-post capillary resistance, and lymphatic drainage. An impermeability of the capillary endothelium serves as a barrier to fluid and protein transudation. This results in a higher gradient between the capillary and tissue oncotic pressure, favoring movement of fluid into the capillary lumen. Paradoxically, the equine digital capillary bed is highly permeable to fluid and macromolecules and is more permeable than the vasculature of the dog and rat paw.⁶ This results in a higher concentration of interstitial protein, favoring edema formation. A high precapillary (arteriolar) resistance and low postcapillary (venous) resistance reduces the capillary pressure, thereby reducing the hydrostatic pressure for transcapillary fluid filtration. The pre-to-postcapillary resistance ratio in healthy horses is comparable with that in other musculoskeletal beds in other species. However, during the prodromal stages of black walnut extract (BWE) and carbohydrate (CHO)-induced laminitis, the relative contribution by the postcapillary portion increases, thus favoring

edema formation.⁷ The third edema safety factor is provided by lymphatic drainage. The small diameter and number of metacarpal lymphatics and the hydrostatic gradient to lymph flow reduce the likelihood that lymphatic circulation can effectively protect the foot against edema when the hydrostatic forces in the capillary favor edema formation.⁷

3. Histopathologic Findings in Acute Laminitis

Histologic study of laminar changes during laminitis has been performed 48–96 h after induction of laminitis with cornstarch or wheat flour gruel. Lameness begins approximately 30 h after administration of the induction ration.⁷ It is difficult to evaluate a progression of lesions by use of these studies because the onset and severity of lameness varies substantially from horse to horse. Studies using these models are further confounded by the fact that approximately 10% of horses seem to be resistant to the ration.

After the onset of lameness, the initial histologic alteration occurs in the digital vasculature, including swelling of the endothelial cells and mild edema formation.⁸ Laminar capillaries become obstructed with erythrocytes within 8 h. Within 6–12 h, a perivascular leukocyte infiltration occurs that then dissipates as the inflammatory cells migrate into the epidermal layer. Arteriolar endothelial cells become deformed as a result of cytoplasm processes that extend into the lumen. Microvascular thrombi and accompanying severe edema formation occur within 24 h, and hemorrhage occurs within the primary dermal laminae within 72 h.

Primary histologic alterations of the laminae occur within 8 h after lameness develops.⁸ Initially, there is thinning and lengthening of the lamellar structures accompanied by reduction, flattening, and displacement of epithelial cells. The secondary lamina become redirected such that lamina nearer the base of the dermal lamina are directed toward the coffin bone, and those nearer the laminar tips are directed toward the hoof wall. Morphologic alterations secondary to epithelial cell damage include swelling, vacuolization, nuclear swelling and/or pyknosis, and leukocyte infiltration of the secondary epidermal lamina, which can be observed as early as 24 h after the onset of lameness.

4. Hemodynamic Events During Laminitis

Garner et al.⁹ introduced the hypothesis that the predominant cause of laminitis after CHO overload was a disturbance in digital blood flow, which occurred during the onset of the syndrome after CHO overload of the gastrointestinal tract. Using contrast radiography, researchers demonstrated reduced perfusion in the terminal vasculature of the foot.¹⁰ Garner et al.⁹ also determined that the changes in digital perfusion are associated with marked systemic hemodynamic changes including a decline in right atrial pressure, diastolic systemic arterial pressure, and systolic systemic arterial

pressure, which reaches a maximum about 16 h after starch is administered through a nasogastric tube.¹¹ This pressure drop is followed by a steady increase in right atrial pressure, diastolic arterial pressure, and systolic arterial pressure. These results suggest that appreciable cardiovascular changes occur in horses with laminitis, and increased release or activation of vasoactive mediators occurs.

The mechanisms responsible for digital hypoperfusion were first evaluated by tracing radioactive albumin particles through the foot during the development of laminitis.¹² A reduction in laminar capillary perfusion and shunting of blood at the level of the coronary band suggests the presence of arteriovenous anastomoses (AV shunts) that open during the development of laminitis, resulting in hypoperfusion of the digital microcirculation.¹² Whereas Allen et al.⁷ demonstrated a reduction in digital blood flow and perfusion at 16 h after experimentally induced CHO overload, Pollitt and Davies¹³ recently demonstrated increases in hoof temperature, suggesting an increase in blood flow to the tissues encased within the hoof capsule. Conversely, Hood et al.¹⁴ demonstrated a decrease in hoof temperature after CHO overload. Hinckley et al.¹⁵ recently used infrared techniques to demonstrate stasis of blood within the hoof during early laminitis. Studies suggest that AV shunts open between the laminar arteries and veins¹⁶ diverting blood flow from the capillaries providing nutrients to laminar tissues, while increasing hoof wall temperature. Collectively, these studies suggest an increase in resistance in the digital circulation (possibly in the venous circulation causing stasis) diverting blood to low resistance shunts. These results illustrate the difficulty of evaluating capillary perfusion by use of temperature data alone.

In subsequent studies using the isolated perfused digit, the specific hemodynamic forces acting on the laminar microcirculation in healthy and experimentally induced laminitic horses have been extensively defined.^{7,17,18} Several alterations in the digital vascular system of horses with experimentally induced Obel grade I laminitis (both CHO overload and BWE models) have been identified.⁷ Of particular importance is the finding that the pre-to-post capillary resistance ratio is decreased in the prodromal stages of laminitis. This imbalance increases the hydrostatic force in the capillary promoting the flux of fluid across the capillary bed within the foot, resulting in laminar edema while capillary permeability remains normal. These findings support the hypothesis that increased venomotor tone initiates laminitis.

Although laminitis induced by either CHO overload or BWE are accompanied by increases in capillary pressure and tissue pressure, differences between the two models have been observed.^{7,18} The severity of the venoconstriction accompanying laminitis induced with BWE was less than that as-

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sociated with CHO overload. These less severe changes with BWE may be because of a difference in the pathophysiology of the disease or because the Starling forces accompanying laminitis caused by BWE were evaluated at a different stage of the disease. Adair et al.¹⁹ recently determined that laminar microvascular blood flow decreases in the first 1–2 h after BWE is administered. This initial decrease is followed by a return of laminar microvascular blood flow to near baseline values. Then, at about 8 h into the disease, laminar blood flow again decreases corresponding to the development of clinical signs of laminitis. The time course of blood flow changes associated with CHO-induced laminitis has not been studied for comparison. More information is needed to determine the relationship between CHO overload and BWE-induced laminitis.

Weiss et al.²⁰ demonstrated a significant increase in platelet-neutrophil aggregates, but not platelet aggregates or clotting times, in ponies administered CHO overload. Furthermore, pretreatment with a platelet aggregation inhibitor prevented laminitis in ponies administered CHO overload, highlighting the importance of these activated cell aggregates in the pathogenesis of laminitis.²¹ Local production of platelet-activating factor within the enterohepatic circulation may result in formation of platelet-platelet and platelet-neutrophil aggregates that lodge in the microvasculature of the digit.

The results of recent studies indicate that normal equine digital and colonic vessels have a substantial capacity for endothelial-dependent relaxation by nitric oxide (NO) *in vitro*, accounting for approximately 70–85% of the maximal relaxation induced by acetylcholine.^{5,22} Furthermore, intravenous infusion of endotoxin to horses for 60 min seems to alter the sensitivity of the digital vascular segments to various endothelium-dependent compounds and reduce the maximal relaxation induced by these compounds.²³ In horses with CHO-induced laminitis, acetylcholine-mediated relaxations of digital vessels *in vitro* are reduced, suggesting that the NO producing capacity of the digital vascular endothelium is reduced, thereby rendering the vessels more sensitive or vulnerable to vasoconstrictive agents. Experimentally, NO donors reduced the lameness and “bounding pulses” of ponies with grass-induced laminitis.²⁴ We have found that infusion of NO into the digital vasculature reduces the vascular changes associated with laminitis.

Endothelins are a family of peptides (ET-1, ET-2, ET-3) produced by various cells that exert numerous biologic and pathophysiologic effects.²⁵ The principal endothelin of importance in vascular diseases or ischemic conditions is ET-1. ET-1 is a potent vasoconstrictor peptide produced by endothelial cells, vascular smooth muscle cells, and macrophages. It not only induces prolonged vasoconstriction in arteries and arterioles but also causes intense profound venoconstriction in both the systemic and pulmonary circulation. Endothelin synthesis is

stimulated by epinephrine, transforming growth factor (produced during platelet aggregation), platelet activating factor (which stimulates platelet aggregation and neutrophil chemotaxis), and tumor necrosis factor,²⁶ which are increased during many diseases in horses characterized by an inflammatory response (pleuropneumonia, endometritis, intestinal ischemia, enterocolitis, anterior enteritis, etc.) and which are empirically linked to the development of laminitis. Katwa et al.²⁷ recently demonstrated that the concentration of ET-1 in laminar connective tissues obtained from experimentally induced, acutely laminitic horses and naturally occurring, chronically laminitic horses were increased compared with a control group.

5. Laminar Basement Membrane Alterations in Laminitis

There is also evidence of mediators that directly damage the laminar basement membrane or epithelial cells. Pollitt et al.²⁸ demonstrated that homogenates of lamellar tissue collected from two horses 48 h after induction of laminitis with CHO overload contained a larger amount of 92-kDa Eq metalloproteinase-9 and 72-kDa Eq metalloproteinase-2, whereas normal horses contained only the 72-kDa Eq metalloproteinase-2. Activation of metalloproteinases could directly damage the lamellar basement membrane. Fontaine et al.²⁹ revealed increased expression of interleukin-1 β mRNA from horses with BWE-induced laminitis. Interleukin-1 β activates vasoactive, procoagulant, and proinflammatory mediators as well as metalloproteinases.²⁹ It is obvious that numerous mediators are present in acutely laminitic horses; therefore, we believe it is unlikely that a single unifying mechanism causes the laminar damage. Most likely, vascular derangement and direct mediator damage coincide.

6. Evidence for the Role of ET-1 in the Pathophysiology of Laminitis

Our laboratory investigated the effects of ET-1 and nonselective ET antagonists on contractile properties of palmar digital arteries and veins collected from normal, non-laminitic horses. In this study, we investigated the hypotheses that ET-1 would cause a marked contraction of arteries and veins, that the response would be greater in veins, and that this contraction could be prevented by pretreatment with ET antagonists. The results of this study demonstrated that ET-1 causes a slowly developing, sustained, and profound dose-dependent contraction of arteries and veins. Digital veins were much more sensitive and responded to a magnitude 3.5 times greater than that observed in arteries. Pretreatment of vessels with either one of the two antagonists caused a dose-dependent blockade of the contraction.

A preliminary *in vitro* vessel study in horses with naturally acquired laminitis has been performed and showed no difference in the response of arteries

or veins to ET-1 between normal and laminitic horses. The ET antagonist was similarly effective in blocking the contractile effects of ET-1 on arteries and veins in both normal and laminitic horses. This data provides evidence that the alteration in laminitic horses is likely an increased synthesis and release of ET-1 rather than an up regulation or expression of endothelin receptors.

To further evaluate the effects of ET-1 and ET antagonists on the response of the normal digital vasculature of horses, we evaluated these substances in an *in vivo* study in conscious horses with a surgically implanted ultrasonic digital flow probe around the lateral palmar digital artery. We investigated the hypotheses that ET-1 infusion into the arterial circulation of horses would cause a dose-dependent reduction in digital blood flow and that this could be prevented and/or reversed with administration of an ET antagonist when infused into the digital arterial circulation as pretreatment or after ET-1, respectively. This study confirmed that ET-1 infusion into the digital artery caused a dose-dependent reduction in digital arterial blood flow. Additionally, at higher doses, ET-1 caused digital pain that was marked in most horses at the highest concentration (10^{-6} M). Pretreatment with a 10^{-5} M concentration of antagonist effectively blocked the ET-induced decrease in digital blood flow. In another experiment in the same horses, a dose-response study of antagonist infusion was performed after digital blood flow was decreased by pretreatment with ET-1. There was a dose-dependent improvement in blood flow, and at the highest antagonist concentration (10^{-5} M), there was a significant improvement in blood flow.

To assess the effects of ET-1 on the digital microvasculature, we have performed a preliminary study of the digital Starling forces in three horses. In this study, we infused ET-1 at a dose comparable with 10^{-6} M into the digital arterial circulation. ET-1 caused a decrease in digital blood flow because of an increase in vascular resistance; the increased vascular resistance was associated with a 30% increase in postcapillary resistance. This suggests venous constriction is an important component of the increase in digital vascular resistance and decreased digital blood flow observed with ET-1 infusion. Capillary pressure increased from 36 to 52 mm Hg.

ET-1 immunohistochemical staining of formalin-fixed, paraffin-embedded laminar tissue specimens from laminitic and normal horses demonstrated intense staining of the arteriolar and venous endothelium and the laminar epithelium and stroma of the sensitive laminae in laminitic horses, but not in normal horses. This information corresponds with previous reports of increased ET-1 expression in laminar tissue of horses with naturally acquired chronic laminitis and in horses with experimentally induced acute laminitis.²⁷

Collectively, the findings from these studies suggest that a local increase in digital vascular and

laminar ET-1 could account for many of the alterations that occur in acute laminitis. We are currently completing studies that use the BWE and CHO models of experimentally induced laminitis to further investigate the potential role of ET-1 in the pathogenesis of laminitis and to test the effectiveness of this ET antagonist. These studies currently focus on measuring digital venous plasma ET-1 concentrations; measuring systemic and digital hemodynamics; monitoring clinical signs; evaluating ET-1 immunohistochemical staining of specimens of laminar tissue and digital arteries and veins; and measuring digital Starling forces in horses administered either ET antagonist or a saline control solution after induction of laminitis. To further demonstrate the potential role of ET-1 in acute laminitis, we have shown increased palmar digital venous plasma concentrations of ET-1 after administration of BWE and CHO. Administration of the ET antagonist locally into the digital artery in BWE horses prevented the characteristic Starling force alterations (increased capillary pressure and vascular resistance) caused by BWE. Horses with naturally acquired and experimentally induced (BWE) laminitis subjectively and qualitatively had increased ET-1 immunohistochemical staining in the laminar epithelium, stroma tissue, and arteriolar and venular smooth muscle and endothelium compared with normal, non-laminitic horses.

Although administration of a low-dose of endotoxin to horses causes a significant decrease in laminar perfusion and digital blood flow, there have been no repeatable models of endotoxemia that consistently induces acute laminitis. However, diseases that are often complicated by laminitis are accompanied by endotoxemia (intestinal strangulating obstruction, anterior enteritis, enterocolitis, pleuropneumonia, and metritis). In a study in our laboratory, we demonstrated a significant decrease in digital arterial blood flow from 30 min to 2 h after administration of a low dose (35 ng/kg over 30 min) of endotoxin to conscious horses. There was a concomitant decrease in digital arterial blood pressure from 30 min to 1.5 h after endotoxin infusion. These digital hemodynamic effects were accompanied by a significant increase in cephalic venous plasma ET-1 concentrations. These findings suggest that perhaps endotoxin does play a role in initiation of the early hemodynamic alterations in laminitis, and that this may be at least partly mediated through increased synthesis and release of ET-1.

Collectively, the findings from these studies clearly suggest a role for ET-1 in the pathogenesis and vascular alterations observed in acute laminitis. The question is whether local ET-1 concentrations increase or whether the ET receptors in the laminae, microvasculature, and palmar digital vasculature are up-regulated, or both. By examining gene expression of ET-1 in these previously collected tissues, we can more specifically and quantitatively determine if ET-1 synthesis is increased in the lam-

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inar tissue. Additionally, evaluation and comparison of laminar basement membrane alterations with alterations in plasma ET-1 concentrations, laminar ET-1 immunohistochemical staining, and ET-1 gene expression will help determine the role and relationship of ET-1 to the laminar basement membrane degeneration characteristic of acute laminitis.

7. Current Treatment of Acute Laminitis

Treatment of laminitis remains empirical and often based on the experience and preference of the clinician. Management of laminitis requires aggressive and appropriate treatment of the primary disease process. Additionally, the cornerstones of treatment of horses with acute laminitis are directed at different components of the pathophysiologic process. Acute laminitis should be considered a medical emergency, and treatment should be instituted immediately after clinical signs develop, or preferentially before the onset of clinical signs. The authors believe the goals of treatment are to eliminate or minimize any predisposing factors, reduce pain, reduce or prevent the magnitude of permanent laminar damage, improve or reverse deleterious digital or laminar hemodynamics, including normalizing digital Starling forces, and prevent further movement of the distal phalanx within the hoof capsule. Considerable controversy exists regarding the treatment of laminitis because of our lack of understanding of the pathophysiology of this disease.

To institute preventive treatment for laminitis, horses at risk must be identified. Many of the primary diseases thought to predispose horses to the development of laminitis are associated with circulating endotoxin. One of the most important preventive measures is to effectively combat the effects of endotoxemia and sepsis by decreasing the severity of the primary illness. Recommended treatments include administration of mineral oil (if engorge on grain), IV fluids, parenteral antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and hyperimmune serum or plasma. Other preventive treatments include heparin, aspirin, vasodilators, corrective hoof trimming and shoeing, placement of the horse in a deeply bedded stall, and frog support. Many of these preventive measures are also instituted therapeutically.

Polymixin B has been used by some clinicians to prevent laminitis in endotoxemic horses, because it forms a stable complex with lipid A thereby preventing endotoxin's interaction with inflammatory cells.³⁰ Administration of polymixin B at 1000, 5000 and 10,000 units/kg did reduce ex vivo production of tumor necrosis factor in horse blood incubated with endotoxin.³¹ However, pretreatment at 2.5 mg/kg did not alter the development of shock, acidosis, or lameness in horses administered CHO overload to produce laminitis.³²

Another drug that has been used to prevent laminitis in endotoxemic horses is pentoxifylline, a methylxanthine derivative with rheologic properties.

Although these latter properties could improve digital hemodynamics, clinical and experimental studies in horses are lacking. Pentoxifylline reduced ex vivo production of cytokines in response to endotoxin and increased prostaglandin I₂ synthesis.^{33,34} Although in vivo benefit of pentoxifylline during endotoxemia was minimal, use with flunixin meglumine improved the efficacy over both drugs alone.^{35,36} More studies are needed to determine the importance of endotoxin in the development of laminitis and the efficacy of drugs to reduce the effects of endotoxin in the prevention of laminitis.

The authors believe one of the most important considerations in developing a preventive and therapeutic plan is to attempt to normalize digital Starling forces. Because of the anatomy of the normal lamina and hoof and the microvascular alterations that develop with the onset of laminitis, horses are highly predisposed to developing marked laminar edema, which leads to compression of the nutrient capillaries, resulting in laminar ischemia, reduction of metabolic waste removal, and ultimately, laminar necrosis and degeneration. Therefore, steps should be made to "normalize" these Starling forces. The best approach to do this is to make sure plasma oncotic pressure is sufficient by supplementing with either plasma or another colloidal solution such as hydroxyethyl starch or plasma. Additionally, care should be taken when administering intravenous fluid therapy to horses with acute laminitis, or those predisposed to develop it, because excessive intravascular volume caused by overzealous fluid administration could have the tendency to perpetuate the development of laminar edema in horses with abnormal digital hemodynamics (i.e., increased capillary hydrostatic pressure). Therefore, the authors suggest that fluid therapy be carefully monitored so as not to administer fluids in excess of the volume needed to maintain normal hydration.

Because it is believed by many clinicians and based on substantial scientific data that the initiating event in laminitis is a vasoconstrictive event, treatments directed at improving digital blood flow and laminar perfusion are often suggested. The authors believe that an ischemic episode caused predominantly by venoconstriction is the initiating event and recommend administration of drugs to cause vasodilation and subsequently improve digital blood flow, Starling forces, and laminar perfusion. The drugs most commonly used to improve digital blood flow are acepromazine (0.03–0.06 mg/kg, q 6–8 h, IM), isoxsuprine hydrochloride (1.2 mg/kg, q 12 h, PO), and topically applied glyceryl trinitrate (2–4 mg/h). The ability of these drugs to improve digital hemodynamics in laminitic horses has not been proven. Our scientific investigations support the role of ET-1 in the early phases of the pathogenesis of acute laminitis, and the demonstration of in vitro and in vivo effectiveness of an endothelin antagonist in preventing or reversing these effects has given the authors some optimism for a potentially

more effective and consistent therapy for improving and maintaining digital blood flow, Starling forces, and laminar perfusion.

With the recent suggestion that vasoconstriction early in the onset of laminitis may have a protective effect by limiting the delivery of gut-derived toxic substances that have direct cellular damaging effects to the laminae, some investigators and clinicians suggest that vasodilation may not be the most appropriate vascular effect in the developmental stages. Based on this information, some investigators and clinicians suggest preventing the vasodilatory events during the developmental phases of laminitis to reduce delivery of these substances to the laminae. Additionally, exercise of an intensity that increases core hoof temperature or local anesthesia of the palmar or plantar nerves result in both hoof wall warming, and by inference, vasodilation; therefore, intense exercise is believed to be contraindicated during the early phases of laminitis. One reportedly effective method for preventing the vasodilatory phase that has been recommended is to soak the feet in crushed ice or cold water. This is a time-honored treatment; however, it would need to be performed continuously and during the developmental phase before the onset of lamellar damage. Otherwise, vasodilation and a rebound hyperemia would occur once the feet are removed from the cold therapy. It is likely impractical to keep the feet sufficiently cold to maintain decreased blood flow because the normal homeostatic mechanisms regulating blood flow may overcome cold-induced vasoconstriction. As is often the situation, the developmental phase (pre-clinical signs) goes unnoticed, and lamellar damage has already occurred by the time treatment is initiated. At this stage, it would be too late to block delivery of cytotoxic substances, and the authors feel that reestablishment of blood flow is important for oxygen and nutrient delivery to the tissues, as well as for removal of potential cytotoxic substances and cellular waste products.

Anti-inflammatory medications are indicated to decrease inflammation, edema, and pain associated with laminitis. Phenylbutazone seems to have the best anti-inflammatory and analgesic effect of any of the NSAIDs commonly used in horses. A dose of 2.2–4.4 mg/kg of phenylbutazone can be administered either IV or PO q 12 h. Alternatively, flunixin meglumine can be administered at 0.5–1.1 mg/kg IV or PO q 8–12 h. A dose of 0.25 mg/kg flunixin meglumine can be administered IV q 8 h to interrupt eicosanoid production associated with endotoxemia. Ketoprofen can be administered at 2.2 mg/kg IV q 12 h. Dimethylsulfoxide (DMSO) is an anti-inflammatory drug that scavenges hydroxyl radicals and decreases edema and is therefore used to counteract the effects of ischemia-reperfusion (I-R) injury. Although the involvement of I-R and oxygen-free radicals in the pathogenesis of laminitis is unclear, the fact that there is a biphasic decrease

in laminar perfusion that normalizes or increases during the intervening period suggests hyperemia and subsequent I-R injury may play a role. The reason DMSO has not been shown to be particularly effective in the prevention or treatment of laminitis could be that I-R injury does not occur or the dose or timing of DMSO used is not appropriate. If used, DMSO should be administered at a dose of 0.1–1.0 g/kg IV diluted in a polyionic fluid with dextrose to a concentration of 10–20%. It can be administered q 8–12 h. Some clinicians prefer to place DMSO topically on the coronary bands.

Because microthrombi and platelet–platelet or platelet–neutrophil aggregates have been shown to form during laminitis, some clinicians prefer to administer heparin and/or aspirin to horses as a preventive or therapeutic agent. Heparin can be administered using several regimens but is often given subcutaneously at a dose of approximately 20,000–40,000 units per 450-kg horse. Heparin leads to microagglutination and a subsequent decrease in packed cell volume.³⁷ There is no evidence that administration of heparin will prevent the onset of laminitis. Aspirin is often administered at a dosage of 10–20 mg/kg PO q 48 h. It irreversibly inhibits platelet cyclooxygenase and therefore production of thromboxane, which should decrease platelet aggregation and vasoconstriction.

Efforts to reduce mechanical forces and stabilize the distal phalanx are imperative to effective treatment of acute laminitis. Horses should not be exercised during the acute stages because this can lead to increased mechanical forces that could lead to shearing of laminae. The stall should be bedded deeply with sand or other material that provides support to the frog and provides some cushion if they spend long periods recumbent. Providing early and effective mechanical support of the distal phalanx can spare weakened, separating lamellae and improve the outcome. This mechanical support should ideally be instituted before or at the onset of foot pain. Frog support is one of the more effective methods of providing support to the distal phalanx. A commercially available moldable thermoplastic material conforms to the shape and sulci of the frog and sole allows for a more effective distribution of the mechanical support to the frog and subsequently the distal phalanx. Care must be taken to fully support the frog but not allow excessive pressure on the sole, because this may increase pain.

Another method to decrease mechanical forces on the distal phalanx is to transect the deep digital flexor tendon to reduce caudal pull on the coffin bone. A deep digital flexor tenotomy has been performed in several horses in acute and chronic stages of laminitis to prevent or reduce coffin bone rotation. Although short-term outcome was promising, the long-term survival and soundness proved to be less successful.^{38,39} The most appropriate use of a deep digital flexor tenotomy may be to perform it in association with corrective trimming and shoeing during

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the chronic stages of laminitis to help reverse the amount of rotation.

Each clinician will undoubtedly develop his or her own therapeutic plan based on current literature and on their past experiences with the effectiveness of these treatments. The information presented above simply represents some of the currently used methods. There are obviously others that have not been discussed that may also have merit. The effectiveness of preventive and therapeutic measures needs to be markedly improved to help manage this devastating disease. This will only become a reality as we collectively work to unravel the remaining mysteries of the pathophysiology of acute laminitis.

8. Prognosis of Horses with Acute Laminitis

Many horses that demonstrate clinical signs of acute laminitis that receive prompt, appropriate medical treatment and mechanical foot support may recover completely. However, some horses, even with mild laminitis, should be withheld from exercise sufficiently until all signs have subsided and only cautiously returned to athletic function. If radiographs demonstrate signs of coffin bone rotation, the prognosis for soundness and even survival must be more guarded. The primary disease that initiates the onset of laminitis also plays an important role in the prognosis and outcome. In general, the greater the degree of coffin bone rotation, the worse the prognosis. Horses with greater than 15° of rotation accompanied by distal displacement into the hoof capsule within 4–6 wk of the onset of laminitis have a poor prognosis. Prolapse of the distal phalanx through the sole is often accompanied by subsolar abscessation. These horses often require extensive, long-term treatment, and the prognosis is grave because of the recurrent, crippling pain and recumbency, which often require euthanasia for humane reasons. In one study of horses with acute laminitis admitted to a university veterinary hospital, 75% did not return to athletic function, and the majority were humanely destroyed within 1 yr because of a lack of response to therapy or development of severe complications.¹

9. Summary

Numerous vascular alterations have been identified in acute laminitis. Vascular derangement may lead to impairment of nutrient deliver to laminar tissue, resulting in necrosis. The balance of microvascular pressure in healthy horses favors edema formation. Therefore, an imbalance in the forces caused by increased venomotor tone could lead to sufficient increases in tissue pressure to collapse capillaries, open arteriovenous shunts, and lead to ischemic necrosis. Further studies are needed to confirm the relationship of the vascular changes to the damage of the laminar tissue so that appropriate therapies can be developed. Investigations in our laboratory provide substantial evidence that ET-1 is involved in the pathogenic cascade with the initia-

tion and propagation of acute laminitis, and may be one area of potential therapy directed at prevention and treatment of this disease. Although current therapies are varied and inconsistent in their effectiveness and typically result in a guarded prognosis, newer, novel, and more effective treatments must be developed as we gain a better understanding of the pathophysiology of this devastating disease.

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