The Role of Vascular Mechanisms in the Development of Acute Equine Laminitis

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ACUTE LAMINITIS has long been attributed to factors or events that precede the onset of laminitis. Between 1759 and 1907 the overconsumption of grain, inflammation of the feet, suppression of perspiration (anhydrosis), excessive rest, excessive bleeding, road concussion, poor shoeing, unilateral weight bearing, sudden environmental temperature changes, prolonged standing (in the cold and aboard ships), diarrhea, and postpartum complications[1-7] were all designated as causes. Today, commonly listed etiologic factors include ingestion of large amounts of grain, cold water, lush grass, or black walnut shavings, repeated concussion, endometritis or other severe infections, colic, exhaustion, stress, drug toxicities, and endocrine dysfunctions.[8-12] At Texas A&M University (Table 1) the factors recorded as the cause presume a causal relationship between some preceding event and the acute laminitis. Logically, any event that precedes laminitis might be a cause, but etiologic validity depends on the definition of "cause" and the role that coincidence might have in the appearance of the disease.

The many "causes" of laminitis have led to the belief that laminitis is a complex disorder brought about by several interacting factors. The current understanding of the pathophysiology of laminitis does not explain how these diverse factors predispose the horse to laminitis. The diagnosis of acute laminitis is based on clinical signs. Because all horses develop similar clinical signs regardless of the cause of laminitis, a common pathophysiologic mechanism is believed to be responsible.

Currently, metabolic abnormalities and endotoxemia are proposed as etiologies of acute laminitis. The metabolic hypothesis[13-17] proposes that laminitis results from derangement of metabolic processes, resulting in structural failure of laminar epithelium. The restriction of histopathologic changes to the epidermal layers and the reduced incorporation of methionine into laminar epithelium of horses with acute laminitis is consistent with decreased keratin metabolism.[17] In this hypothesis inflammation, mechanical collapse of the digit and vascular pathologies occur as secondary events.

The endotoxemia hypothesis proposes that lipopolysaccharides enter the systemic circulation[11,18] and produce a digital circulatory failure either directly[18] or via a Shwartzman-type reaction.[19] The role of endotoxins in the laminitis syndrome is not well defined. Some investigators[8,11] support an active etiologic role for endotoxins, particularly in cases of laminitis that follow gastrointestinal or septicemic crises. A direct etiologic role for endotoxins in laminitis[9] has been questioned because of failure of injected or infused endotoxins to induce acute laminitis.[20-22]

The presence of warm feet with a bounding digital pulse suggest that a vascular component is active in laminitis.[18,23-25] Some investigators believe that blood is pooling in the digits, whereas others hypothesize that blood is inhibited from entering the digits during the acute disease. Several investigators[12,24-27] have observed that ischemia or reduced blood flow to the foot occurs in laminitis. Ischemia initiates a complex cascade of events that result in loss of tissue function. Included as a primary event in this cascade is necrosis due to anoxia.

A second component of the ischemic cascade is the occurrence of reperfusion injury. Reperfusion injury is damage to an organ that occurs when blood flow resumes after a period of ischemia.[28] Most of this injury is attributed to peroxidation of cellular and intracellular lipid secondary to the production of superoxide radicals. This process is described elsewhere.[29,30]

In addition to the damage attributable to anoxia and that caused by reperfusion injury, other events accompany ischemia. Alterations occur in the ability of cellular and noncellular elements of the blood to flow through the microcirculation (hemorrheologic dysfunctions). Coagulopathies, activation of leukocytes, and loss of vascular endothelium all occur frequently in postischemic

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TABLE 1. Reported Causes of Laminitis at the Large Animal Clinic and the Laminitis Research Laboratory Between 1978–1987*

Reported Cause	Number	Percent of Total
Unknown	253	48.2
Grain overload	64	12.2
Gastrointestinal (Colic/diarrhea)	60	11.4
Trauma	34	6.5
Road founder	30	5.7
Pasture founder	20	3.8
Pulmonary disease	10	1.9
Hoof trimming	8.5†	1.6
Drug induced	8	1.5
Hoof infection	7	1.3
Systemic infection	6	1.1
Moldy hay	5	0.9
Metritis	3.5†	0.67
Deworming	3	0.57
Water ingestion	2	0.38
Edema	2	0.38
Myositis	2	0.38
Pheochromocytoma	1	0.19
Alfalfa hay	1	0.19
Miscellaneous	5‡	0.95
Total	525	100.00

* The designation of cause was that recorded on the admission form or stated in the clinical history.

† One case in which cause was stated as being either one of two simultaneous events.

‡ Represents cases in which more than two events were listed as potential causes.

tissues.[31] The order of these changes and their importance to tissue survivability is still in question and is currently the focus of continuing research.

It is unclear in laminitis if vascular changes initiate the lameness, or if they result from some other mechanism, or if they are coincidental to the disease. This article will collate and organize data regarding the vascular component of laminitis.

Definition of Temporal Phases

Developmental and acute laminitis are terms used in this article to separate laminitis into temporal phases based on clinical signs. Developmental laminitis occurs in that period between initiation of mechanisms that result in the disease and appearance of acute lameness. In both experimental models and clinical patients, the developmental phase lasts a maximum of 72 hours.[25]

Acute laminitis, as used in this article, begins with the onset of the characteristic lameness and ends with mechanical collapse of the digit. Mechanical collapse results in a long-term medical problem and thus signals the onset of chronic laminitis. If collapse does not occur, the acute phase lasts 72 hours,[25] at which time the laminitis in most nontreated animals begins to undergo resolution and healing.

We will discuss the histologic, hemodynamic, and pharmacologic data about the vascular changes in developmental and acute laminitis. Data used in this article are all described relative to the first appearance of lameness. The mechanisms of secondary changes such as displacement of the third phalanx, digital sepsis, epithelial hyperplasia, and hyperkeratinization will not be considered in detail in this article.

Histopathology of Developmental and Acute Laminitis

Studies describing the morphologic changes accompanying laminitis focus on changes occurring after lameness has been present for 72 hours to 7 months. Few studies describe changes present prior to or coincident with the onset of lameness. Histopathological studies by Linford,[26] Obel,[32] Mostafa,[33] Marks,[34] Roberts et al,[35] Kameya et al.[36] and ongoing Hoof Project research form the basis for the summary of histopathological changes of equine laminitis.

Following the onset of lameness, the initial histological change appears in the digital vasculature (Fig 1). As early as 4 hours following lameness, changes include a swelling of the endothelial cells and limited edema.[33,34] Erythrocytic congestion and obstruction of the laminar capillaries are present within 8 hours.[33,34] A perivascular infiltrate appears by 6 to 12 hours and then decreases as leukocytes migrate to the epidermal layers. Arteriolar endothelial cells are deformed by cytoplasmic processes extending from the luminal surface.[34] Microvascular thrombi and severe edema appear within 24 hours,[33,34] and hemorrhage in the primary dermal lamina occurs within 72 hours.[32–34]

These changes are not considered vasculitis because there is no persistent inflammatory infiltrate of the vessel wall.[37] The vascular changes are similar to histological changes seen in hemorrhagic shock-induced vasoconstriction[38] and pure vasospastic diseases in people.[39] Of particular note is the presence of endothelial bridges in acute laminitis,[34] similar to those induced by cell-to-cell contact following intense vasoconstriction.[40]

Anatomic distortion of the lamina occurs as early as 8 hours after lameness. There is a thinning and lengthening of lamellar structures accompanied by reduction, flattening, and displacement of the epithelial cell layers.[26,32–34] Additionally, a redirection of the secondary lamina occurs such that the lamina nearest the base of the dermal lamina are directed toward the third phalanx, and those nearer the laminar tips are directed toward the wall.[33] These changes are consistent with the distal and palmar movement of the third phalanx relative to the coronet and wall as the digit fails mechanically.[41] Additional mechanical distortion is likely as submural edema induces compression of soft tissues.[34]

Morphologic changes attributable to epithelial cell damage include swelling,[32–34] vacuolization (hydropic degeneration),[32–35] nuclear swelling and/or pyknosis,[32,33] and leukocytic infiltration[32] of the secondary epidermal lamina. These changes appear within 24 hours of lameness. Atrophy and degeneration of the spinous and basal cells of the secondary epidermal lamina and appear

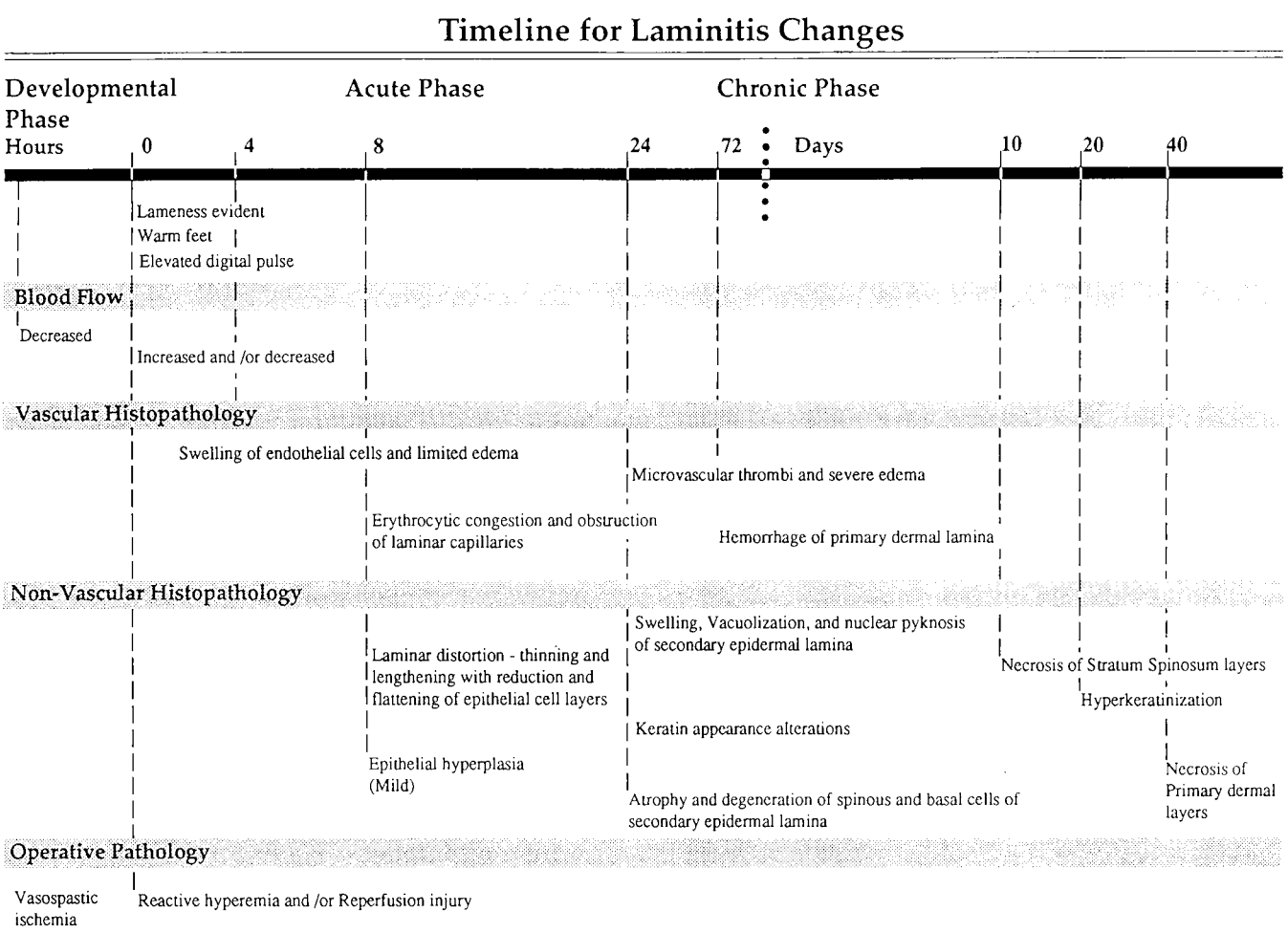

FIG. 1. Temporal correlation of clinical, hemodynamic, and histopathologic changes occurring in laminitis. Changes have been normalized to the initial appearance of lameness.

within 24 hours.[32–35] Necrosis of the stratum spinosum and dermis, although present early, becomes a distinct feature at 10 days and 40 days, respectively.[33,35] These epithelial changes are nonspecific. Cellular swelling, hydropic degeneration, and pyknotic nuclei are changes consistent with ischemic and/or toxic damage to cells but do not reflect a specific etiology.[42] Leukocytic infiltrates in the acutely affected horse with laminitis are consistent with both postischemic and toxic mechanisms.[39,43,44]

Epithelial hyperplasia is evident within 8 hours and is not uniformly distributed.[32–34] Hyperplasia is most notable in regions nearest the base of the primary dermal lamina and reflects an apparent splitting of basal cells into two distinct populations (a stem cell and committed cell pool) and an increase in the number of the spinous cell layers. Decreased onychogenic substance associated with decreased synthesis, swelling, and cessation of the bundling of keratin fibers have been reported as early as 24 hours.[33,34] Hyperkeratinization is notable after 10 to 20 days.[33,35,36] The laminar epithelial hyperplasia and hyperkeratinization seem to be secondary to vascular and mechanical damage. This interpretation is based on the observation that the angiopathy precedes the nonvascular changes and that both hyperplasia and hyperkeratinization are sequelae to the loss of cell-to-cell contact inhibition.[45] The histological appearance of hyperplasia after 8 hours is somewhat surprising but may indicate that the precipitating event has passed by the time the acute disease is manifest.

In summary, the histopathologic changes present in the distal digit of the horse with acute laminitis reflect three general ongoing processes: an angiopathy, a mechanical distortion of the dermal-epidermal tissues, and a physiopathologic response in the affected tissues. Of these three processes, the angiopathy histologically precedes the other two.

The Hemodynamic Data

There are limited data about the digital circulation in the developmental phase compared with the acute and early chronic phases. Digital blood flow, using hoof wall temperature as an index of flow in laminar areas,[46] has been assessed at 4-hour intervals from the time the horse was

clinically normal until acute laminitis became evident. The temperature initially dropped but increased to above control values with the onset of lameness. These data are similar to that of people with cutaneous vasoconstriction secondary to hypovolemia.[47] If hoof wall temperature reflects blood flow, then a reduction in digital flow prior to lameness is suggested. In isolated, denervated digits of anesthetized horses in the developmental phase of laminitis, there is an increase in capillary and tissue pressure, vascular compliance, and postcapillary resistance, and a decrease in total digital blood flow.[27,48]

Digital blood flow in the acute phase of laminitis is not well defined. There are reports indicating flow is increased[23] or decreased[24] or decreased at the capillary level while the total flow is increased via arteriovenous shunts.[23,46] The responsiveness of the palmar digital arteries and veins in laminitis has been reported to be decreased during the acute phase.[49] Assuming that the study of hemodynamics in the acute phase of laminitis is accurate, the contradictory data can be explained by viewing digital blood flow as either a function of severity of the disease or as a progressive sequence of vascular changes.

Digital perfusion in acute laminitis can vary depending on the severity of the initial insult. In mild insults the vascular architecture is maintained and blood flow through the digit varies as a function of inflammatory response. In severe insults, the vascular architecture is partially or totally destroyed when there is mechanical failure of the digit. In the mild insult, an initial increase in blood flow is thus possible, whereas a decreased flow is expected in the more severely affected foot.

Assuming that some digital vascular patency is maintained, digital perfusion can vary with time as physiologic responses to the initial insult occur. Assessment of the digital circulation soon after appearance of lameness often shows an increased flow and decreased vascular resistance, consistent with a reactive hyperemia. If assessment is made later in the course of the disease process, i.e., at a predefined degree of lameness, a decreased perfusion appears as edema, coagulopathies, altered hemorrheology, and reperfusion injury occur.

Pharmacological Studies

We reviewed data on drugs that alter the severity of laminitis when used in the developmental or acute stages. Two classes of drugs, steroids and alpha adrenergic blocking agents, have *in vivo* or *in vitro* effects. Studies by Eyre *et al.*[50] showed that corticosteroids potentiate contractility of digital arteries from normal horses. The *in vitro* studies were followed by chronic administration of high doses of triamcinolone and testosterone.[51] These drugs alone did not cause laminitis. However, when horses were fed carbohydrate overload diets after steroid treatment, the resulting lameness was more severe than in those not receiving steroids.[51]

Alpha adrenergic blocking agents have been used in both the developmental and acute stages of laminitis. Phenoxybenzamine is the primary drug used for laminitis studies.[52] As a preventative, alpha adrenergic blockade with phenoxybenzamine prevents laminitis. When phenoxybenzamine is used as a treatment for acute laminitis in the carbohydrate model, i.e., after the onset of lameness but before mechanical failure, only 1 of 25 horses developed chronic disease. A third study by Volker[53] tested phenoxybenzamine in naturally occurring laminitis under field conditions. In this later study, alpha adrenergic blockade showed a protective effect when administered as a preventative and therapeutic effect when given to the patient in the acute phase.

These pharmacological data support the concept that laminitis is a primary vascular disease. Steroids, which potentiates vascular contractility, increases the severity of the laminitis, implying a vascular component. The clinical effectiveness of alpha adrenergic blockade strongly supports a vascular component in laminitis and implies that a vasoconstrictive mechanisms is operative.

Discussion

The histologic, hemodynamic, and pharmacologic data reviewed support a major role for ischemia of the distal digit as the primary event in acute laminitis. Three hypotheses are offered to explain the ischemia. Hunt[54] proposes that the initial insult is an increase in the postcapillary resistance caused by digital venoconstriction. The digital venoconstriction is thought to result in intradigital edema via increased transcapillary movement of fluid. The resulting edema, trapped behind the hoof wall, induces an increased submural tissue pressure resulting in a decreased digital blood flow. These events are accompanied by an opening of arteriovenous shunts and the secondary formation of microvascular thrombi, ischemia, and pain. A second hypothesis, offered by Pollitt,[55] contends that there is hypothalamic mediation of prolonged dilation of digital arteriovenous shunts. Ischemic necrosis and associated pain occurs because the blood is being shunted away from the metabolically active epidermal structures of the submural lamina.

A third hypothesis contends that laminitis results from peripheral vasospasm that induces ischemia of the digit followed by reactive hyperemia and reperfusion injury.[12,56] This hypothesis proposes that an inappropriate stimulation or response of the vascular smooth muscle of the digit results in a sustained contraction. The intensity and duration of the vasospasm produces varying degrees of digital ischemia. When the vasospasm resolves, there is increased digital blood flow because of reactive hyperemia. The duration and intensity of the vasospasm determines the intensity of the clinical signs. If the episode was mild, the horse may have a stronger digital pulse, increased digital temperatures, and pain during

reperfusion, and then recover. If the vasospasm was severe, the subsequent metabolic and supportive dysfunctions lead to digital collapse. Ischemia and reactive hyperemia is followed by reperfusion injury. During the ischemic period, changes in the biochemistry of the epidermal cells occur. On reoxygenation these changes result in the formation of oxygen radicals.[29] Oxygen free radicals, present either as free oxygen or as hydroxyl form, are cytotoxic. Cytotoxicity is, in part, secondary to peroxidation of cell lipids and proteins.[29] Reperfusion injury, coupled with neutrophil influx, an impaired hemorrheologic status, and microthrombosis can more severely damaged the digit than the period of ischemia and can lead to mechanical failure of the digit.

The vasospasm hypothesis is consistent with the clinical signs seen in laminitis. There is no lameness during the period of decreased blood flow in the developmental phase. This is similar to the paraesthesia experienced by 20% of individuals with iliac arterial occlusion,[57] acute vasospastic disease of the digits in people,[58] or when one's leg "goes to sleep" while sitting in a position that restricts perfusion to the limb. Tingling or pain occurs with restoration of tissue perfusion. If this corollary is correct, pain becomes evident in the horse with acute laminitis when reperfusion occurs. The increased digital temperatures and bounding digital pulses observed in acute laminitis are consistent with the reactive hyperemia following transient vasospastic occlusion.[59] This hypothesis is supported by the histopathological changes of an angiopathy and a reactive hyperemia. The secondary edema, red cell aggregates, and coagulopathies associated with reperfusion of ischemic tissues[29] are histologically present in the horse with acute laminitis.

If we accept vasospasm as a common pathway of laminitis, we need to ask why only the digits are involved. Selective vasospasm of digital cutaneous tissues is not restricted to the horse. Raynaud's phenomenon[56] in people is characterized by transient episodes of ischemia that bilaterally affect the distal digits of the hands and occasionally the feet. Initially, the digits are white, and there is a regional numbness attributed to vasospasm. In the second phase, the fingers are cyanotic because of deoxygenated blood in the cutaneous venous plexus. The third, or red, phase is attributed to reflex hyperemia accompanied by pain, warmth, and throbbing of the fingers. With recurrent episodes of Raynaud's phenomenon the nail plate becomes thinner proximally and ridged. Additionally, there can be ulcerations, infections, and hypertrophy of the chronically affected digits. The mechanism of Raynaud's phenomenon is not fully understood, but transitory vasospasm is a central mechanism.[56]

The nature of the vessels to the digit predisposes the horse to regional vasospastic ischemic disease. The arterial supply to the digital cutaneous circulation is an arterial plexus formed by primary, secondary, and tertiary branches of the palmar digital arteries. The arteries have thick, muscular walls with relatively small lumens[55] and are unable to autoregulate,[60] changes that predispose to sustained contraction. Numerous arteriovenous shunts associated with the specialized microcirculation of the digital papilla and submural lamina[61,62] can redistribute blood away from metabolically active tissue. Blood flow through the normal digital microcirculation can be greatly reduced by only slight alterations in the Starling forces acting across the exchange vessels.[63]

If vasospasm is the final common pathway of laminitis, then it should be possible to relate the designated causes of laminitis to a vasospastic state. In 48.2% of the horses (Table 1) with laminitis there was no identified cause. In this group are horses where the cause was not known by the owner, not identified in the clinical history, or not recorded in the medical record. Of the 51.8% with a designated cause, 17.85% were associated with nutritional factors, 13.8% with trauma, 12.5% with hypovolemic states and/or shock, and 4.25% with sepsis. How can these events be linked to inappropriate stimulation or response of the digital circulation?

Feeding refined carbohydrates or amine-containing food can result in stimulation of the cardiovascular system.[64,65] Additionally, enteric bacteria can produce enterotoxins *in vivo* (as opposed to endotoxins) that mimic the activity of vasoactive peptides.[66] Our studies support a role for the production of vasoactive amines and peptides by cecal microflora incubated with the carbohydrate substrate that induces laminitis. Similar vasoactive amines are present in the normal equine digit and are probably vascular neurotransmittors. Thus it can be hypothesized that in laminitis of nutritional origin, vasoactive agents of nutritional or enteric microfloral origin enter the circulation and preferentially affect the digital circulatory bed.

There is speculation that digital trauma can result in ischemia secondary to the formation of submural edema. Because the digit is enclosed within a relatively rigid wall and sole, it is predisposed to vascular compression secondary to tissue swelling. As in closed head injuries, swelling of the brain compromises vascular function by simple compression of the veins and then the arteries. A second pathway suggest a central role for vasospasm of the digital vessels following trauma. Operators of jackhammers, sanders, and typewriters develop a vasospasm of the digital circulation[67,68] which is seemingly analogous to "road founder" laminitis. The proposed mechanism is the development of a hypersensitivity of the digital vascular smooth muscle.

Hypovolemia, shock, and sepsis are potential causes of digital ischemia. Sepsis or hypovolemic shock results in a poor perfusion of cutaneous microcirculations.[69] This low flow state is the product of insufficient intraluminal pressure and/or vasoconstriction (hypovolemia) or dilatation (sepsis) of the cutaneous circulation. This is

especially important in a microcirculation that does not autoregulate well. It could also be hypothesized that the bacteria responsible for the sepsis could, like the enteric bacteria, produce vasoactive compounds capable of causing digital vasospasm.

Thus, most causes of laminitis can, in theory, be coupled to lameness through mechanisms that induce ischemia. Until proven by well-designed studies, the interconnection between specific causes and the onset of ischemia will have to remain a theoretical link.

The apparent role of a vasospastic-ischemic mechanism in acute laminitis has several implications. The absence of clinical signs during the developmental phase and the transitory nature of vasospasm makes prevention of laminitis difficult. Direct prevention is limited to using vasoactive compounds which promote enhanced digital perfusion. Because regulation of digital hemodynamics is critical to the normal biomechanical, nutritional, and thermoregulatory functions of the digit, it would be inappropriate to routinely use such agents in all horses. Currently, drug treatment must be restricted to horses in high-risk categories, and then only for a short time. If vasospastic-ischemia causes laminitis, treatment of the acutely affected horse should focus on limiting the severity of lesions. Treatment should include the use of vasoactive agents, such as the alpha adrenergic blockers, that increase digital cutaneous perfusion and of agents that limit the severity of reperfusion injury.

The short acute phase (4 to 60 hours) unfortunately means that most horses with laminitis are already in the chronic phase when they are first seen for treatment. Histologically, hyperplasia of laminar epidermal basal cells and evidence of structural failure of the digit are present within 8 hours after lameness develops. Thus, the nature of laminitis leads to the caveat that most horses with laminitis are seen after pharmacological manipulation can be of significant benefit. Continued studies on rehabilitation of the chronically affected horse will be necessary in spite of a better understanding of the inductive mechanisms.

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