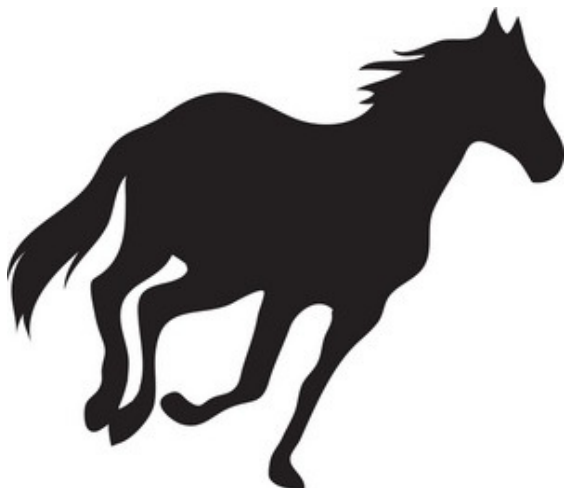

Therapy With or Without Hyperbaric Oxygen

Determining the Best Treatment for
Laminitis in Horses

Prepared for:
Horse Illustrated

In partial fulfillment of Mrs. Susan
Eller's English 303 Technical Writing Class

Prepared by: **Kristi Marie Butler**



February 8, 2012

Abstract

The purpose of this report is to recommend to *Equine Journal* readers the best treatment option for horses afflicted with Laminitis. I analyzed two available solutions: treatment without hyperbaric oxygen therapy and treatment with hyperbaric oxygen therapy. I evaluated each treatment method based on the average costs involved with each type of treatment, the accessibility and longevity of each treatment, and the side effects of each treatment.

My research methodology began with general research to gain a better understanding of available treatments for Laminitis. After general research, I established criteria to evaluate the treatment options and conducted further, more specific research. I interviewed a farrier, Mr. Heith Norred, about shoeing horses, and a veterinarian, Dr. Jay Warford, about medicinally treating afflicted horses. I also emailed a veterinarian, Dr. Henry Steve Adair III, regarding hyperbaric oxygen therapy. Once all the information was gathered, I analyzed it and chose the better treatment option.

Initial treatment with hyperbaric oxygen therapy(hyperoxia) ranges in price from \$700-\$4,200, depending on the severity of the case. Initial treatment without hyperbaric oxygen therapy costs around \$100. Unless the horse and owner happen to reside nearby a facility that offers hyperbaric oxygen therapy, treatment without hyperoxia is more easily accessed. Both treatment options require further therapy after the initial treatment, however, the duration of the continuing treatment after hyperoxia is shorter than the duration of the treatment without hyperoxia. Treatment without hyperbaric oxygen therapy has a higher propensity for adverse side effects; treatment with hyperoxia has negligible side effects.

Hence, I recommend treatment with hyperbaric oxygen therapy as the better treatment option for horse owners attending to working horses ailed with Laminitis.

P.O. Box 2727
Ruston, LA 71272
February 8, 2012

Elizabeth Moyer, Editor *Equine Journal*
P.O. Box 8237
Lexington, KY 40533

Dear Ms. Moyer:

Enclosed within this letter you will find my analytical research recommendation report for determining the best treatment option for working horses stricken with Laminitis. For my research, I compared the two treatment options available: treatment without hyperbaric oxygen therapy and treatment with hyperbaric oxygen therapy.

I analyzed the two solutions based on the average costs involved with each type of treatment, the accessibility and duration of each treatment, and the side effects of each treatment. After analyzing the data, I determined that treatment supplemented with hyperbaric oxygen therapy makes the better treatment option. Horses who receive this therapy endure the pain from Laminitis for a much shorter duration, thereby enabling the horse to return to work faster. Hyperbaric oxygen therapy also does not have the adverse side effects that may arise with traditional medicinal treatment.

I appreciate the opportunity to research and recommend a treatment option for your readers. I look forward to submitting more articles to you as I continue my research in the field of veterinary medicine.

Sincerely,

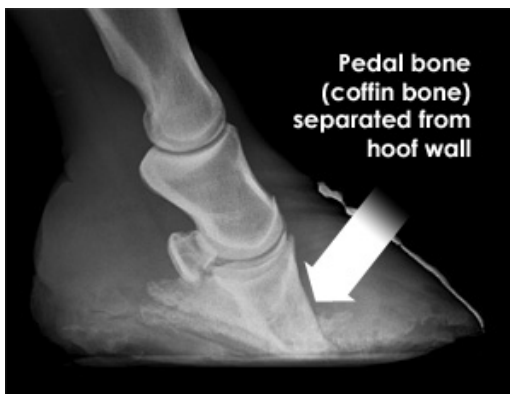
Kristi Marie Butler

Table of Contents

Introduction.	1-3
Research Methodology.	4-6
Solutions and Criteria.	7-8
Results.	9-11
Analysis and Conclusions.	12
Recommendation.	13
Works Cited.	14
Appendix A.	15-18

Introduction

Laminitis is a disease that affects the hooves of horses and impairs the stricken animal's mobility. The outermost part of a horse's hoof consists of keratin, a hard structure with no blood supply. This tough, protective layer encapsulates the inner, living tissue of the hoof. Inside the hoof lies the last bone in the leg, the distal phalanx (also referred to as the third phalanx, P3, or the colloquial term, coffin bone). A thin, extremely sensitive layer of tissue called the laminae surrounds and suspends the bone in the correct position within the body of the hoof. The laminae consists of nerves, arteries, and veins, and it provides the living tissue with the vital blood supply. Any issue with circulation to the laminae will lead to death of the tissue within the hoof capsule. Necrotic tissue* causes abscesses to form, and since the blood supply to the hoof is limited, the abscesses require extensive therapy in order to heal correctly. In severe cases of Laminitis, the distal phalanx can actually rotate out of the proper positioning within the hoof, sometimes to the extent of the bone protruding through the bottom of the hoof and exposing itself to the outside. Rotation, or sinking, of the bone is also know by the colloquial term "founder". Although the terms founder and Laminitis are often used interchangeably, technically Laminitis can cause founder, but a horse will not founder without first having the onset of Laminitis (Van Oldruitenborgh-Osterbaan). The photographs below show an x ray image of a hoof with Laminitis on the left and an x ray image of a healthy hoof on the right.



"Laminitis & PPID." *Prascend*. Web. 29 Jan. 2012.



"Client Services - Virginia Equine Imaging." *Home - Virginia Equine Imaging*. Web. 29 Jan. 2012.

Veterinarians classify Laminitis as either mechanical or systemic, depending on the factors that trigger the onset of the disease. External factors that pull the hoof wall away

*Necrotic tissue is tissue that is no longer living, but is still attached to a living organism's healthy tissue.

2

from the bone and distort the hooves' shape, such as an injury or poor trimming, cause mechanical Laminitis. Some examples of external factors include horses whose feet persistently hit hard surfaces through habitual pawing, horses ridden over hard ground, and infections in the hoof wall. Farriers trim horses' hooves around once every eight weeks to maintain the proper hoof shape. If a horse goes an extended period of time without trimming, the toe of the hoof will continue to grow, causing the heel of the hoof to drop. This "long toe, low heel syndrome" results in the horses' bearing more of its weight more in the heel of the hoof instead of evenly distributed throughout the hoof. Consequently, the hoof wall essentially peels away from the coffin bone. Besides the external factors that instigate Laminitis, various internal factors can also instigate Laminitis (Van Oldruitenborgh-Osterbaan).

When internal factors affect circulation within the laminae, systemic Laminitis afflicts the horse. Systemic Laminitis originates from one of three reasons: problems with metabolism, classical inflammation, or an injury that causes increased and then decreased blood supply to the laminae. A metabolic disturbance initiates the onset of systemic Laminitis. Rapid change in diet (feed or roughage) easily disturbs a horse's normal metabolism. For example, the high levels of protein, nutrients, and sheer volume of the first grass of spring differ starkly from the lower levels that exist in the sparsely available winter grass. A horse turned out to graze freely with unlimited supply of grass will often develop Laminitis. The levels of protein in the grass also change during autumn when the grass begins to brown. The metabolic abnormalities that arise from the change in diet lead to improper cell functioning, and these metabolic abnormalities also lead to the activation of proteases*(Pollitt).

In addition to metabolic issues, classical inflammation can also cause systemic Laminitis. The body reacts to anything foreign, such as pathogens or a foreign object like a splinter, through inflammation. The immune system utilizes inflammation in an attempt to prevent the compromising of the integrity of the horse's health; inflammation serves as a mechanism to isolate and eliminate anything recognized as foreign to the body. However, inflammation also causes aggregation of leukocytes, or white blood cells, in the area near the foreign body. Leukocytes destroy harmful cells, but they can also engulf and destroy living tissue, resulting in laminae failure (Hood DM.).

The third issue resulting in systemic Laminitis is an injury that causes increased and then decreased blood flow to the laminae. Technically termed "ischemia-reperfusion injury," researchers believe this type of injury relates closely to inflammation. The complexities of this issue go beyond the scope of this article, but essentially the injury first restricts blood circulation, then increases blood circulation. This changing of blood flow can cause

*Proteases, or proteolytic enzymes, cleave cells in the bloodstream to activate them. For example, The protease rennin cleaves angiotensinogen, a powerful vasoconstrictor, to become its active form angiotensin and raise blood pressure. If angiotensin is activated when the organism does not need a rise in blood pressure, problems will arise.(Berg 253-256).

3

a myriad of byzantine afflictions, including Laminitis (Pollitt). For additional information about the pathology of ischemia-reperfusion injuries, see the article in Appendix A found on pages fifteen through eighteen.

In order to recommend the best treatment option for horse owners, I analyzed two treatment methods for Laminitis: treatment without hyperbaric oxygen therapy and treatment with hyperbaric oxygen therapy. I evaluated the two based on the average costs involved with each type of treatment, the accessibility and longevity of each treatment, and the side effects of each treatment. For my research I performed the following tasks 1) gain a better understanding of available treatments for Laminitis, 2) establish criteria for analyzing the treatment options, 3) obtain information from secondary sources regarding hyperbaric oxygen treatment and treatment without hyperbaric oxygen, 4) interview Mr. Heith Norred for prices and information from the point of view of the attending farrier, 5) interview Dr. Jay Warford for prices and information from the point of view of the attending veterinarian, 6) Email Dr. Henry S. Adair, III, for information regarding hyperbaric oxygen therapy, and 7) analyze all information gathered.

Through my research, I found that that although the hyperbaric oxygen therapy (hyperoxia) costs more than treating the horse without hyperbaric oxygen, hyperoxia has far less adverse side effects than treatment without hyperbaric oxygen. Hyperoxia therapy also significantly shortens the duration of the disease and lessens the amount of time the horse suffers from Laminitis.

In this analytical research recommendation report, I will expound my research methodology, efficient solutions to the problem, and the criteria I used to analyze the two solutions. Then, I will present the information from my research and give my recommendation based on conclusions I drew from my analysis.

4

Research Methodology

To determine the best treatment option, I executed the following:

1. Gain a better understanding of available treatments for Laminitis.
2. Establish criteria for analyzing the treatment options.
3. Obtain information from secondary sources regarding hyperbaric oxygen treatment and treatment without hyperbaric oxygen.
4. Interview Mr. Heith Norred for information from the point of view of the attending farrier.
5. Interview Jay Warford, DVM, for information from the point of view of the attending veterinarian.
6. Email Henry Steve Adair III, DVM, for information regarding hyperbaric oxygen therapy.
7. Analyze all information gathered.

Task 1

I spoke with my employer at the vet clinic, Dr. Jay Warford, and he suggested researching Laminitis. He told me about issues and treatments he encountered during his internship with horses, and he also addressed the prevalence of the disease. Dr. Warford also suggested researching hyperbaric oxygen therapy as a treatment option. To gain a better understanding of Laminitis and treatment methods available, I conducted general research online.

Task 2

I chose to compare the two solutions based on the average costs involved with each type of treatment, the accessibility and longevity of each treatment, and the side effects of each treatment. Cost efficiency obviously needs consideration; if the cost of the treatment is higher than the value of the horse, then in most cases the owner would opt for an alternate method of treatment. I analyzed both the accessibility of the treatment and longevity of the treatment. For example, if the afflicted horse must travel hours to reach the nearest hyperbaric oxygen chamber and board overnight for a week, the convenience factor of staying close to home will more than likely play a factor in the decision of which treatment to use. I decided to also evaluate any adverse side effects from the treatments in making my recommendation.

5

Task 3

I found information regarding the process and effects of hyperbaric oxygen therapy primarily online through the University of Tennessee College of Veterinary Medicine's website and through Louisiana State University School of Veterinary Medicine's website. Veterinarians on staff at the universities wrote a number of articles about hyperbaric oxygen therapy. I consulted both the *Equine Veterinary Journal* and the *Journal of Equine Veterinary Science* for a large portion of my information on treatment options without hyperbaric oxygen. These journals also provided articles with information regarding treatment with hyperbaric oxygen.

Task 4

I interviewed Mr. Heith Norred about different cases of Laminitis he has encountered. As a third generation cowboy and a farrier, Mr. Norred has an immense amount of experience with horses suffering from Laminitis. He primarily provided me with a specific price for both corrective shoeing and preventative shoeing.

Task 5

I interviewed Dr. Jay Warford about different cases of Laminitis he has treated over the years. He has owned his own veterinary practice for eleven years, and before opening his own business he worked as an intern for an equine veterinarian. He primarily provided me with specific prices for drugs commonly used to treat Laminitis and the method of treatment he follows.

Task 6

After searching through secondary sources for costs involved with hyperbaric oxygen therapy and finding little information, I decided to contact a clinic that administers the treatments. I found a website and an email address for Dr. Adair, and he answered my questions to provide me with the information I needed to evaluate the costs associated with hyperbaric oxygen therapy.

Task 7

After sufficient research, I studied and analyzed all the information I had compiled to decide whether treatment with or without hyperbaric oxygen therapy would be the best option. During my analysis, I considered costs involved with each treatment, the locations of hyperbaric oxygen chambers, durations of each treatment, and side effects the horse experiences during and after treatment. However, I found through my research that horse owners utilize hyperoxia treatments for things other than medicinal purposes, such as to increase fertility or to maximize athletic performance. Some companies sell hyperbaric oxygen chambers to private veterinary practices or to facilities with large horse operations. Because of the widespread using of the chambers, it is impossible to pinpoint the exact locations of the chambers and the accessibility of the chambers (Equineox).

Solutions and Criteria

I amassed my research in order to ascertain which treatment option – treatment with or without hyperbaric oxygen therapy – would be best for horses suffering from Laminitis. In this section, I will state the two solutions I analyzed and the criteria I selected to evaluate the solutions.

Solution

I chose the two treatment options available for Laminitis: traditional treatment without hyperbaric oxygen therapy and treatment with hyperbaric oxygen therapy.

Treatment Without Hyperbaric Oxygen Therapy:

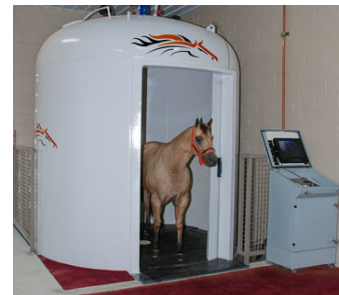
Typical treatment for Laminitis includes long term corrective shoeing and short term NSAIDs to manage pain and reduce inflammation (Warford). Once the horse has shoes and pain medication, the coffin bone stops rotating and the healing process begins. The corrective shoes help properly distribute the horse's weight and return the coffin bone to its original position within the hoof (Treatment). The image to the right shows a picture of a type of corrective horseshoe.



Imprint Plus for Next Stage Recovery for Laminitis.
2011. Photograph. www.imprintshoes.co.uk.
Web. 6 Feb. 2012.

Treatment With Hyperbaric Oxygen Therapy:

Hyperbaric oxygen therapy administers high dosages of oxygen at an increased atmospheric pressure to the afflicted patient. The patient is lead inside of the hyperbaric chamber, and once inside the sealed off machine, the operator manipulates oxygen levels and air pressure inside of the chamber. Hyperbaric oxygen therapy causes a significant rise in the levels of oxygen in the blood, thus increasing cellular metabolism and decreasing healing time. This increase in cellular metabolism enhances the effects of drugs administered at the time of the therapy. “Hyperbaric oxygen therapy is both a primary treatment and a complementary therapy. Consequently, hyperbaric oxygen therapy may be used alone or in conjunction with conventional therapies” (Adair). The image on the right shows a patient inside of a hyperbaric oxygen chamber.



Treatments: Hyperbaric Oxygen Therapy. 2009.
Photograph. *The Sanctuary: Equine Sports Therapy and Rehabilitation Center.* FAEP.
Web. 6 Feb. 2012.

Criteria

I evaluated the two treatment options based on average costs involved with each type of treatment, the accessibility and duration of each treatment, and the side effects of each treatment.

Cost:

I determined costs for treatment without hyperbaric oxygen therapy based on figures from the vet clinic where I work and from my interviewing Mr. Heith Norred. I found costs for hyperbaric oxygen therapy from emailing Dr. Henry Steve Adair, III, a veterinarian who administers the treatments.

Accessibility and Duration:

I evaluated accessibility of each treatment based on location and the average duration of each treatment.

Side Effects:

I analyzed any adverse side effects that could possibly arise from either of the two treatment methods, including toxicities from over dosage of medication. I also considered other factors such as stress the horse endures from traveling.

9

Results

In this section I will present the findings of my research on both the treatment option without hyperbaric oxygen and the treatment option with hyperbaric oxygen.*

Treatment without Hyperbaric Oxygen

Cost:

Typically treatment without hyperbaric oxygen includes corrective shoeing and NSAIDs, most commonly phenylbutazone, as needed. One tube of phenylbutazone, more commonly known by its trade name Bute, lasts around one month and costs \$17.44. The attending veterinarian may also prescribe Dimethyl sulfoxide (to increase soft tissue absorption of medications) for \$7.83, acepromazine (a sedative) for \$24.96, and isoxsulpine (a vasodilator) \$30.00 (Warford).

The price for collective shoeing typically falls in the range of \$60-\$175 per shoeing, depending on the severity of the case and the individual horse. For six months up to a year, the farrier should come every four to six weeks to change the shoes and to trim the horse's hooves. Since horses that contract Laminitis likely will relapse, after finishing the corrective shoeing therapy most horses require regular horseshoes as a preventative measure. Farriers charge \$50-70 for a regular shoeing, and they shoe healthy horses every six to eight weeks (Norred).

Accessibility and Duration:

Most equine veterinarians offer mobile service to their clients for a fee. For this reason, clients can easily access their vets when needed. Based on my experience and discussions I have had with other horse owners, clients can also easily access their farriers for treatment.

Horse owners administer non-steroidal anti-inflammatory drugs (NSAIDs), to help alleviate their horse's pain, but typically after one to two months, the inflammation has lessened to a degree that does not necessitate medication. If the attending veterinarian prescribes Dimethyl sulfoxide (DMSO), the horse's owner will either apply the medication topically or inject the medication intravenously two to three times daily for one month. The ailed horse will take Isoxsulpine pills twice daily for six to fourteen weeks (Warford).

*Each case of Laminitis is different. Facts and figures presented in the "Results" section depict averages for the typical case of Laminitis.

The afflicted horse wears corrective horseshoes for six months up to one year, and many horses require regular horseshoes after the corrective shoeing therapy because they cannot go barefoot without relapsing (Norred).

Side Effects:

Side effects of the medicines involved with the treatment of Laminitis rarely occur if the owner doses drugs correctly as prescribed by the attending veterinarian.

Administering NSAIDs will upset the horse's sensitive gastrointestinal tract over time, and this irritation of the intestines can lead to secondary issues such as colic. High amounts of these drugs in the horse's bloodstream also stress the liver and kidneys; these organs filter toxins from the bloodstream (Treatment).

DMSO administered topically can cause skin irritation or even blistering, making the horse unwilling to allow the owner to easily apply the medicine. The horse may also experience mild sedation and drowsiness. Owners can also inject DMSO intravenously directly into the horse's bloodstream. If DMSO is not diluted with fluids or is injected too fast, intravenous injection of DMSO can cause destruction of red blood cells (Dimethyl).

Side effects from Isoxsuprine and Acepromazine rarely afflict horses, but can include allergic reactions. Studies have shown that high amounts of both of these drugs will not result in any lasting toxicity or harmful effects to any organs (Rose, Allen, and Khonhe).

Treatment with Hyperbaric Medicine:

Costs:

The prices for a therapy session in a hyperbaric chamber vary by location. Typically, the prices fall in the range of \$100-\$300 per session. Horses with Laminitis undergo seven to fourteen treatment sessions in the chamber; the number of sessions depends on the individual case. Horses usually require additional treatment to make a full recovery, such as corrective shoeing and trimming (Adair and Geiser).

Accessibility and Duration:

Through my general research browsing universities' websites, I found that horse owners can access hyperbaric oxygen therapy for their horses through several of the twenty-nine vet schools in the United States, including the veterinary schools in Ohio, Iowa,

Louisiana, and New York. However, in addition to medicinal therapy, hyperbaric oxygen therapy also has substantial benefits for the athletic and breeding horses. Because of these benefits, companies sell hyperbaric oxygen chambers commercially to clients and private veterinary practices, making it difficult to produce a specific number of chambers available (Equineox). Patients usually require therapy once a day for one to two weeks (Adair, Henry S.).

Dosage of oxygen, frequency, and duration of therapy depend on the individual case. As Drs. Adair and Geiser from the University of Tennessee explain in one of their articles, “For example, a protocol might call for a patient to receive 2 atmospheres of pressure (like diving 33 ft. in the ocean) for 1 hr. every other day for 7-10 treatments” (Adair III). In another case, Tom Scherder, a rehabilitation specialist who owns and operates Pegasus Equine Performance facility in Union, Kentucky, successfully treated a horse once a day for ten days. (Thomas)

Side Effects:

Veterinarians associate minimal risks with the administering of hyperbaric oxygen therapy. According to the attending veterinarians on staff at the University of Tennessee College of Veterinary Medicine, “As with any drug therapy, there are occasions where unanticipated reactions occur, but these are rare. The side effects in animals are very infrequent” (Adair, Henry S.). Hyperoxia, hyperbaric oxygen therapy, is one of the safest therapeutics when used appropriately (Slovis). If the patient’s therapy session lasts too long or the pressure inside of the chamber rises too high, then the patient has the propensity to come out of the chamber in a dazed and stunned state from too much oxygen reaching the brain. However, this dazed effect wears off shortly with no lasting effects on the patient (Warford).

Analysis and Conclusions

Analysis

Cost:

Initial treatment with hyperbaric oxygen therapy (hyperoxia) ranges in price from \$700-\$4,200, depending on the severity of the Laminitis case. Each treatment session typically costs between \$100 and \$300. Initial treatment without hyperbaric oxygen therapy costs around \$100, depending on the attending veterinarian's prices. Both treatments require corrective shoeing after the initial treatment; this initial shoeing costs \$60-\$175. For treatment without hyperbaric oxygen therapy, every four to six weeks for six months up to one year the patient needs new shoes. For treatment with hyperbaric oxygen therapy, the horse does not need to wear corrective shoes for this extended period of time; generally after eight to twelve weeks the horse does not require the corrective shoes (Adair and Geiser).

Accessibility and Duration:

Unless the horse and owner happen to reside nearby a facility that offers hyperbaric oxygen therapy, treatment without hyperoxia is more easily accessed. Equine veterinarians generally offer mobile services where they will drive to see their patient. Without hyperbaric oxygen treatment, it would take a horse six months up to one year to make a full recovery from Laminitis (Warford). With hyperbaric oxygen therapy, the patient makes a full recovery in one to two months (Adair and Geiser).

Side Effects:

Treatment without hyperbaric oxygen therapy has a higher propensity for adverse side effects than treatment with hyperbaric oxygen therapy, partly because of the lengthy duration of the treatment without hyperbaric oxygen therapy. Shortening the time it takes for a patient to complete treatment and rehabilitation lowers the capacity for negative side effects to ail the patient. Horse's treatment with hyperoxia has an extremely low risk, and any side effects that can arise have no lasting effects on the patient.

Recommendation

For working horses suffering from Laminitis, I recommend horse owners opt for treatment with hyperbaric oxygen therapy. Hyperoxia therapy shortens the time that the horse suffers from Laminitis by up to ten months. Hyperbaric oxygen therapy does not cause the detrimental side effects that treatment with traditional medicine can cause. A shorter recovery period for a horse with Laminitis will help prevent secondary issues from afflicting the patient. For locations of hyperbaric chambers within traveling distance, the horse owner should contact his or her local veterinarian.

While I do recommend this therapy for working horses that need to heal from Laminitis and return to work, for pleasure horses I would recommend traditional therapy. Hyperbaric oxygen treatments cost a substantial amount of money for a horse that is not generating an income for the owner. The afflicted horse will eventually recover if properly managed.

Works Cited

- Adair, Henry S., DVM, and Dennis R. Geiser, DVM. "Putting the Pressure on Disease." *The University of Tennessee College of Veterinary Medicine*. Web. 09 Jan 2012.
- Adair III, Henry Steve. "Hyperbaric Oxygen Therapy." Message to the author. 3 Feb. 2012. E-mail.
- Berg, Jeremy M., John L. Tymoczko, and Lubert Stryer. "Chapter 9: Catalytic Strategies." *Biochemistry*. 7th ed. New York, NY: Macmillan, 2012. 253-66. Print.
- "Dimethyl Sulfoxide – DMSO." *EquiMed*. Ed. Mariea Lefere. Mark Sellers, 8 May 2009. Web. 1 Feb. 2012.
- "Equineox Technologies – Hyperbaric Oxygen Therapy Chambers for Equine Veterinarians." *Equineox*. Equineox Technologies Limited, 2004. Web. 01 Feb. 2012.
- Hood DM. Laminitis as a systemic disease. *Vet Clin North Am Equine Pract*. 1999 Aug; 15(2):481-94, viii. Review. PubMed PMID: 10472123.
- Norred, Heith. "Farrier Prices for Founder." Telephone interview. 28 Jan. 2012.
- Rose, R.J., J.R. Allen, D.R. Hodgson, and J.R. Kohnke. "Studies on Isoxsurprine Hydrochloride for the Treatment of Navicular Disease." *Equine Veterinary Journal* (1983): 238-43. *Pubmed.gov*. PubMed. Web. 01 Feb. 2012.
- Slovis, Nathan. "Hyperbaric Oxygen Therapy." *Equine Disease Quarterly* 18.1 (Jan 2009). *UKAg Gluck Equine Research Center Department of Veterinary Science*. Maxwell H. Gluck Equine Research Center. Web. 02 Feb. 2012
- Thomas, Heather S. "Hyperbaric Oxygen Therapy for the Equine Athlete." *Equine Chronicle* Jan/Feb (2008). Web. 2 Feb. 2012.
- "Treatment of Laminitis." www.equine.vetmed.lsu.edu. Equine Health Studies Program, 1997. Web. 9 Jan. 2012.
- Van Oldruitenborgh-Osterbaan, M. M. Sloet. "Laminitis in the Horse: A Review." *Veterinary Quarterly* 21.4(1999): 121-27 Taylor & Francis Online. PubMed Web of Science. 28.12. 1 Nov 2011. Web. 9 Jan. 2012.
- Warford, Jay, DVM. "Veterinarian Prices for Laminitis." In Person. 28 Jan 2012.

Appendix A

ISCHEMIA-REPERFUSION INJURY

Anthony T. Blikslager, DVM, PhD, Diplomate, American College of Veterinary Surgeons

Department of Clinical Sciences, North Carolina State University

Intestinal ischemia/ reperfusion injury in veterinary species

Although the majority of research into basic mechanisms of intestinal ischemia/ reperfusion injury has been performed on rodents and cats, the principal veterinary species affected clinically by this disease process is the horse. According to a recent national survey, approximately 4% of horses have an episode of colic annually, with a case fatality rate of 11%. Colic is the leading cause of mortality in horses, and strangulating obstruction is one of the principal causes of colic associated deaths in horses. For example, in a multi-year referral hospital-based study, 21% of horses referred for evaluation of colic had strangulating-obstruction and 75% of these horses died, whereas of the 31% of horses that had simple obstruction, only 25% died. Although survival of horses undergoing surgery for strangulating obstruction has recently dramatically improved, these data indicate that approximately twice as many deaths are associated with strangulating intestinal obstruction compared with simple intestinal obstruction. Horses with intestinal diseases other than strangulating obstruction may also suffer from ischemic disease. For example, horses suffering from long-term simple obstruction will ultimately succumb to ischemic necrosis as increasing intraluminal pressure progressively occludes the circulation within the intestinal wall. Decompression of these lesions may result in reperfusion injury.

Strangulating obstruction versus low-flow ischemia

While the horse is an excellent species for clinical studies of strangulating obstruction, because of the relatively high prevalence of this disease process, horses are not an easy species to use for research, and funding for equine research is limited. Therefore, the majority of research has focused on treatment of ischemia/ reperfusion injury based on mechanisms elucidated in other species, particularly the cat. In addition, because many of the feline studies were conducted using low-flow ischemia, equine studies have also been conducted using this mechanism of inducing ischemia. However, mucosal ischemic injury associated with clinical strangulating obstruction has some distinct differences from low-flow ischemia. During strangulating obstruction, there is a disparity in blood flow, rather than a uniform reduction in blood flow, in which the venous circulation is occluded prior to the intestinal arterial blood supply because of the differences in vessel wall thickness and compliance. This results in a hemorrhagic lesion, in which the arteries continue to pump blood into the tissues for a variable length of time, before they ultimately collapse as a result of increases in tissue interstitial pressure. Therefore, it is unknown whether mechanisms that apply to low-flow ischemia are also applicable to

strangulating obstruction. For example, in studies on pigs and horses with strangulating obstruction, the degree of reperfusion injury that was induced was relatively small compared to the level of injury that occurred during the ischemic phase. This is in contrast to reperfusion injury following low-flow ischemia, in which reperfusion injury is typically severe, compared to the minimal level of injury that occurs during the ischemic phase. The reason for these differences is likely the rapid onset of injury during strangulating obstruction, with near-maximal injury by the time tissues are reperfused, whereas low-flow ischemia appears to prime tissues for reperfusion injury, while inducing limited injury as a result of continued low level blood flow.

Comparative aspects of reperfusion injury

There are a number of distinct similarities between ischemia/ reperfusion injury in equine jejunum and colon compared to that documented in laboratory animals and cats. For example, it has been shown that equine small intestine contains xanthine dehydrogenase, an enzyme that has been found to be critical to the ischemia/reperfusion injury cascade in feline studies. Feline studies documented the conversion of xanthine dehydrogenase to xanthine oxidase during lowflow ischemia, which generated superoxide during early reperfusion. This in turn led to the formation of chemoattractant molecules responsible for inciting infiltration of neutrophils; the final common mediator of reperfusion injury. Similarly, in equine jejunum, xanthine dehydrogenase was converted to xanthine oxidase during ischemia. Furthermore, it has been shown that mucosal injury in both the equine jejunum and the colon is exacerbated during reperfusion of low-flow ischemia, associated with infiltration of neutrophils. However, a number of distinct differences between species exist, and a number of questions remain unanswered. For example, it is unclear which mucosal enzymes might be responsible for initiation of reperfusion injury in the equine colon, since xanthine oxidase is absent. It is possible that other oxidant generating enzymes, such as aldehyde oxidase, are capable of triggering reperfusion injury, or that very low concentrations of xanthine oxidase within the microvasculature might be sufficient to trigger reperfusion injury. There are also other comparative differences in xanthine oxidase distribution. For instance, xanthine oxidase is virtually absent in neonatal jejunum in the human, horse, and pig. Interestingly, research on piglets has shown a lack of reperfusion injury under a variety of conditions, suggesting that xanthine oxidase may indeed have a critical role in reperfusion injury, as has been shown in feline studies. In addition to species-specific differences, mucosal xanthine oxidase levels are also dependent on the segment of intestine studied. In general, the highest levels of this enzyme are present within the proximal small intestine, diminishing distally so that relatively low levels are present in the ileum. However, it is unclear if these differences region-specific differences in oxidant enzyme concentrations result in different levels of reperfusion injury. Another important aspect of reperfusion injury is the presence of neutrophils. Although a number of early studies indicated that infiltrating neutrophils incited reperfusion injury, close examination of mucosal reperfusion injury in cats indicated that neutrophils resident within the mucosa, rather than infiltrating neutrophils, were most critical to initiation of reperfusion injury. Here again there are species differences. For example, the horse appears to have very low numbers of resident

neutrophils within the mucosa. The conclusions to be made from all of this information is that distinct differences in the level of reperfusion injury that occurs following an ischemic event may exist between species, so that application of mechanisms learned from one species should be applied to other species cautiously

Alternative Mechanisms of Reperfusion Injury

It is important to note that there are probably other mechanisms of reperfusion injury aside from injury induced by reactive oxygen metabolites and neutrophils. For example, one equine study showed marked mucosal metabolic abnormalities induced by ischemia, including mitochondrial dysfunction, which persisted during reperfusion because of the inability of tissues to regain normal function. Therefore, reperfusion injury may in some cases simply be a time-related continuation of injury initiated during ischemia. This type of injury might warrant an entirely different therapeutic approach, including provision of soluble and highly metabolizable nutrients. Studies on pigs subjected to strangulating obstruction have also noted delayed reperfusion injury, occurring 6-18-hours following the initial ischemic event, in which reparative tissues are injured by neutrophils migrating across restituting epithelium. These events appear to be dependent on superoxide and neutrophil integrin binding, since further injury was inhibited by treatment with superoxide dismutase or anti-CD11/ CD18 monoclonal antibody at the time of reperfusion.

Lessons learned from therapeutic trials in horses

Although in most clinical scenarios it is not possible to intervene prior to an injurious event; an understanding of the mechanisms of reperfusion injury has provided the potential for inhibiting further injury at the time of resolving an ischemic lesion. This potential was heightened by early studies on reperfusion injury suggesting that the majority of injury took place during the reperfusion phase rather than during ischemia. Therefore, many studies have been performed, including experimental trials in horses, to assess pharmacologic inhibitors of oxidant generating enzymes and neutrophil infiltration. Although a number of therapeutics appear to markedly reduce injury in experimental ischemia/ reperfusion injury in laboratory animals, this has not translated into useful clinical therapies for treatment of veterinary species to date. Of the pharmacologic agents that have been evaluated for their efficacy at reducing reperfusion injury, some generalized statements can be made. Perhaps the most widely used anti-oxidant medication in veterinary medicine, DMSO, has had uniformly poor results at ameliorating intestinal injury, and cannot be recommended for the purpose of reducing intestinal injury in clinical cases based on this experimental evidence. Other agents that have shown minimal benefit in a number of studies include U-74389G, a 21-aminosteroid, allopurinol, and antagonists of PAF. The most promising results for treatment of reperfusion injury have been obtained when using solutions containing an array of anti-oxidants, nutrients, and vasodilatory agents. Initial trials with these solutions involved administration via mesenteric arteries, which would preclude their use clinically. However, more recent studies have shown the ability of these solutions to ameliorate injury when instilled intraluminally, providing a potentially clinically

applicable treatment for reperfusion injury. However, further trials will be required in order to determine if such solutions reduce injury associated with strangulating obstruction.

SELECTED REFERENCES

1. Blikslager AT, Roberts MC, Rhoads JM, Argenzio RA. Is reperfusion injury an important cause of mucosal damage after porcine intestinal ischemia? *Surgery* 1997; 121:526-534.
2. Dabareiner RM, White NA, Donaldson LL. Effects of intraluminal distention and decompression on microvascular permeability and hemodynamics of the equine jejunum. *Am J Vet Res* 2001; 62:225-236.
3. Gayle J, Jones SL, Argenzio RA, Blikslager AT. Neutrophils increase paracellular permeability of restituted ischemic-injured porcine ileum. *Surgery* 2002;132:461-470.
4. Laws EG, Freeman DE. Significance of reperfusion injury after venous strangulation obstruction of equine jejunum. *J Invest Surg* 1995; 8:263-270.
5. Moore RM, Muir WW, Bertone AL, Beard WL, Stromberg PC. Effects of dimethyl sulfoxide, allopurinol, 21-aminosteroid U-74389G, and manganese chloride on low-flow ischemia and reperfusion of the large colon in horses. *Am J Vet Res* 1995; 56:671-687.
6. Prichard M, Ducharme NG, Wilkins PA, Erb HN, Butt M. Xanthine oxidase formation during experimental ischemia of the equine small intestine. *Can J Vet Res* 1991;55:310-314.
7. Van Hoogmoed LM, Nieto JE, Snyder JR, Harmon FA. In vitro evaluation of an intraluminal solution to attenuate effects of ischemia and reperfusion in the small intestine of horses. *Am J Vet Res* 2002;63:1389-1394.
8. Young BL, White NA, Donaldson LL, Dabareiner RM. Treatment of ischaemic jejunum with topical and intraluminal Carolina Rinse. *Equine Vet J* 2002; 34:469-474.