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Prevention of Reexpansion Pulmonary Edema and Ischemia–Reperfusion Injury in the Management of Diaphragmatic Herniation

Andrew J. Worth, BVSc, MACVSc
Roslyn G. Machon, BVSc(Hons), MVSc, MS, MACVSc, DACVA
Massey University Veterinary Teaching Hospital
Palmerston North, New Zealand

ABSTRACT: Before the 1980s, the veterinary literature reported a guarded prognosis for traumatic diaphragmatic herniation (TDH) in dogs and cats. In recent years, a better understanding of the pathophysiology of this condition has led to changes in the perioperative management of patients with TDH as well as significant improvements in patient outcome. Reexpansion pulmonary edema (RPE) and ischemia–reperfusion (IR) injury are now recognized as potentially fatal complications of surgical correction of TDH. Potentially fatal RPE appears to be a greater risk in patients with chronic lung collapse, and cats are affected more often than dogs. To prevent RPE, no attempt should be made to fully or rapidly reinflate collapsed lung lobes during surgery to minimize barotrauma. IR injury can occur when blood flow returns to previously strangulated and ischemic organs and may play a role in the development of RPE. Resection of ischemic tissue before reperfusion prevents metabolites of anaerobic metabolism from initiating a cascade of cellular injury and may be valuable in certain cases of abdominal organ entrapment occurring with diaphragmatic herniation. Research continues into effective strategies and medical therapies for prevention of RPE and IR injury.

The phenomenon of pulmonary edema following reexpansion of a collapsed lung was first described in humans in the mid-19th century.[1] By 1902, it was well recognized that copious sputum production and respiratory distress may follow thoracic drainage in humans presenting with pleural effusion. Physicians at the time also noted that the onset of respiratory distress in these patients was often preceded by a symptom-free period of minutes to hours and that the phenomenon usually occurred only after rapid drainage of large volumes (>2 L in adult humans) of fluid from the pleural space.[1,2] In 1958, Carlson et al[3] reported five cases of pulmonary edema following rapid relief of pneumothorax in the medical literature. In the 27 years following Carlson's publication, 50 additional human cases were reported, and nine of these patients died.[4]

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Reexpansion pulmonary edema (RPE) is now well recognized as a rare but life-threatening complication of thoracic drainage in humans. Most mild cases resolve spontaneously following symptomatic therapy; serious cases are managed with advanced respiratory therapy using double-lumen endotracheal tubes, independent lung ventilation, and positive end-expiratory pressure; however, deaths still occur.[4,5]

In 1965, Walker and Hall[6] first drew attention to the risk for pulmonary edema in dogs and cats undergoing surgical correction of traumatic diaphragmatic herniation (TDH). Pulmonary edema was attributed to forcible reexpansion of "firmly" collapsed lung lobes. TDH is associated with lung collapse both before and during surgical correction. A ruptured diaphragm allows abdominal viscera to enter the thoracic cavity, displacing the lungs and preventing full lung expansion. Visceral-to-parietal pleural contact is further compromised as hemorrhage from torn blood vessels or exudation from entrapped organs collects within the pleural space. Once the elastic recoil of a compromised lung lobe is exceeded, collapse ensues and alveoli are no longer inflated during inspiration, resulting in ventilation–perfusion mismatch and shunting. These problems are compounded by the loss of mechanical function of the diaphragm, concurrent chest-wall trauma, and pain, all of which contribute to hypoventilation.[7]

Complete restoration of effective ventilation is ultimately achieved only by herniorrhaphy; however, surgical correction should be delayed while attempting to stabilize the patient (this was discussed in detail in a companion article[8]). During herniorrhaphy, the injury-associated lung collapse is exacerbated by surgically induced pneumothorax, but intubation and delivery of intermittent positive pressure ventilation (IPPV) maintain effective ventilation. However, IPPV may play a role in the development of RPE.

Ischemia–reperfusion (IR) injury is a syndrome associated with temporary ischemia of tissue. Conditions associated with the development of IR include gastric dilatation-volvulus (GDV) and strangulation of viscera through a hernia.[9] In TDH, the most commonly herniated organs (i.e., the liver, small intestine, spleen)[10] can suffer from partial vascular obstruction at the level of the diaphragmatic defect. When oxygenated blood ceases to flow through tissue, cell metabolism switches from the aerobic pathway to the anaerobic pathway to continue to supply the energy needs of the cells. Returning these organs to the abdomen allows reperfusion of stagnant capillary beds and sinusoids. This may liberate potentially toxic by-products of anaerobic metabolism, such as unbuffered acids, potassium, and lysosomal enzymes.[11] Liberation of metabolites that damage endothelial linings is a potential secondary cause of pulmonary edema in patients with TDH. The collapsed lung lobes are also subjected to IR injury. Mitigating the effects of IR injury should lead to improvements in patient outcome.

ISCHEMIA–REPERFUSION INJURY

The aptly titled "oxygen paradox" refers to the relatively minor damage caused by initial ischemia of tissue compared with severe cellular damage resulting when oxygen is reintroduced by the return of circulation.[11] The pathophysiology of IR injury was recently reviewed in the veterinary literature by McMichael and Moore.[12]

The pathogenesis of reexpansion pulmonary edema is complex and probably multifactorial. Mechanical stresses, surfactant abnormalities, neutrophil accumulation, ventilator-induced injury, and ischemia–reperfusion injury may all contribute.

In brief, so-called reactive oxygen species (ROS), such as superoxide anions, hydroxy radicals, and hydrogen peroxide (H_2O_2), are generated in tissues as the result of ischemia and incomplete reduction of molecular oxygen.[11] ROS may be derived from marginating neutrophils or via xanthine oxidase pathways in hypoxic cells. Neutrophils produce various oxidizing agents by reducing molecular oxygen in a process called *the respiratory burst*, which is accompanied by increases in superoxide anion and H_2O_2 (i.e., ROS). During periods of tissue ischemia, hypoxanthine accumulates from the degradative pathway of ATP (Figure 1). Following reperfusion and return of oxygen to the tissue, xanthine oxidase oxidizes hypoxanthine, generating superoxide radicals (O_2^-). In turn, these radicals are dismutated to H_2O_2 by superoxide dismutase. H_2O_2 is not a free radi-

cal, but with rapid reduction in the presence of iron, it is further metabolized by the Haber-Weiss reaction to form reactive hydroxyl radicals (OH^-). Many ROS are free radicals—molecules with unpaired electrons in their outer orbits. Through interaction with membrane lipids, ROS can form self-perpetuating chains of toxic hydroperoxides that damage cell membranes, leading to cell death.[11,12] Xanthine oxidase, an intracellular enzyme that produces superoxide during reoxygenation injuries in some species, is not thought to be important in humans because of low or absent tissue levels. The major derivation of ROS—neutrophils or xanthine oxidase—likely varies by species and tissue type.[13]

Reperfusion failure (the no-reflow phenomenon) can result from interstitial edema, thrombosis and neutrophil margination, postischemic hypotension, and increased blood viscosity.[8,11] In general, the extent of reflow is inversely proportional to the duration of ischemia, and outflow (venous) obstruction appears to be more problematic than does inflow obstruction.

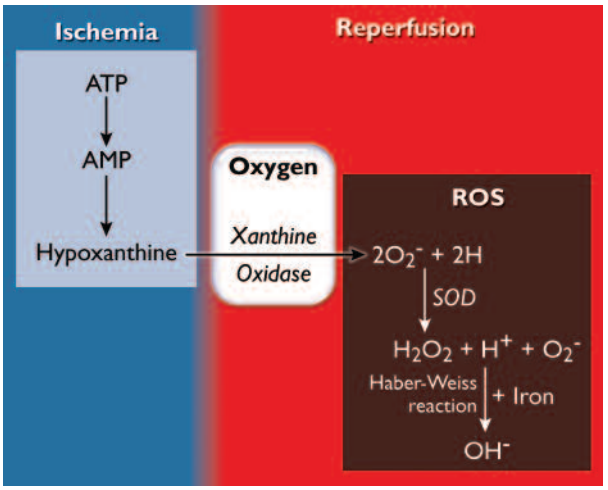

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Figure 1. Diagram depicting the formation of reactive oxygen species (ROS) from the anaerobic pathway of mitochondrial ATP. Following reperfusion and the return of oxygen to the tissue, xanthine oxidase oxidizes hypoxanthine, generating superoxide radicals (O_2^-). O_2^- is dismutated to hydrogen peroxide (H_2O_2) by superoxide dismutase (SOD). In the presence of iron, H_2O_2 is further metabolized by the Haber-Weiss reaction to form hydroxyl radicals (OH^-).

REEXPANSION PULMONARY EDEMA

Pathogenesis

Most authors agree that the pathogenesis of RPE is highly complex and probably multifactorial. Various mechanisms have been proposed for the formation of protein-rich, noncardiogenic pulmonary edema in RPE. These mechanisms include mechanical disruption of vessels resulting from negative intrapleural suction pressures used for reexpansion of the collapsed lung, surfactant abnormalities, changes in pulmonary artery pressures as a result of lung reexpansion, and a direct effect of hypoxia on vascular permeability.[14–17] Most of these proposals focus on mechanisms by which fluid filtration from alveolar capillaries is increased as a direct result of negative interstitial pressure, resulting in edema. However, although the generation of large, negative intrapleural pressures has been shown to result in RPE under experimental conditions (thereby supporting the concept of mechanical disruption of alveolar capillaries),[1] clinical cases of RPE have been reported following lung reexpansion in the absence of pleural suction.[4] Loss of surfactant activity has been reported[18] in atelectatic human lungs and has also been documented[1] in a goat model of RPE. Abnormalities in surfactant production or function may therefore contribute to the phenomenon of RPE. However, other investigators documented[17] normal inflation characteristics in rabbits with previously atelectatic lungs and collected normal surfactant from rabbits subjected to 7 days of unilateral lung collapse. The absence of ventilation (not oxygenation) has been shown to cause RPE compared with anoxic ventilation (with nitrogen) in a rat model.[18] The effect was attenuated by the addition of surfactant to the collapsed lungs before reinflation. The mechanical stimulus of alveolar inflation is thought to be a major stimulant of surfactant production. In the absence of ventilation, insufficient surfactant may result in increased airway pressure necessary to achieve alveolar inflation during reexpansion; thus damage to the epithelial cells may result. Barotrauma from assisted ventilation is traditionally associated with extraalveolar air accumulation and tension pneumothorax but has been shown to increase wet-lung weights in experimental studies.[19] Alterations in lung fluid balance, increases in endothelial and epithelial permeability, and severe tissue damage have been observed following mechanical ventilation in animals.[19] Extensive hemodynamic studies[20] in rabbits with evidence of RPE failed to document right atrial or pulmonary artery pressures that could account for edema formation, whereas hypoxia was shown to have no significant effect on alveolar capillary permeability in an isolated canine lung preparation.

In 1988, Jackson et al[17] proposed a potential role of IR injury in the pathogenesis of RPE. In 2002, Suzuki et al[21] suggested that RPE is the result of an inflammatory response and that neutrophil aggregation and degranulation in a reinflated lung is an important pathologic mechanism in this condition. Activated neutrophils are a potentially major source of superoxides and long-lived oxidants. However, in a rabbit model[15] of RPE, chemically induced neutropenia attenuated but did not prevent edema formation despite reduced numbers of alveolar neutrophils. Current thought focuses on the importance of increased alveolar capillary permeability as the common pathologic endpoint in RPE, suggesting that this increased permeability results from a combination of capillary membrane disruption and IR-mediated injury.[22] Reperfusion injury may be linked to the development of ROS following reoxygenation of previously ischemic lung tissue.

Forcible reexpansion of the lungs to evacuate air from the thoracic cavity at the conclusion of herniorrhaphy is no longer recommended.

The Role of Ischemia–Reperfusion Injury

The biochemical mechanisms that operate in RPE are thought to be analogous to IR injuries described in other tissues, including the heart, kidneys, brain, and intestine.[2,17] IR injury has been identified as the main cause of primary graft failure during human lung transplantation.[23] The autoregulatory mechanisms of the pulmonary vasculature provide total or near total cessation of pulmonary blood flow during periods of atelectasis.[24] It has been shown in a canine model that atelectasis can result in a 72% reduction in pulmonary blood flow through the affected lung.[25] This potential for hypoxia is exacerbated by the lack of alveolar ventilation in the collapsed lung and resorption of alveolar air—the major source of oxygen for alveolar epithelial and endothelial cell function.[17] Reexpansion of the collapsed lung allows resumption of alveolar ventilation and perfusion, resulting in rapid reoxygenation of the previously hypoxic lung tissue and potential reperfusion injury. Xanthine oxidase is known to be one of the main sources of ROS and to be upregulated in the lungs by hypoxia and/or reoxygenation.[26] The intracellular hydroxyl and H_2O_2 scavenger dimethylthiourea has been found to be effective in reducing RPE in a rabbit model.[17]

Pulmonary reexpansion was recently shown to induce production of ROS and then apoptosis of alveolar (i.e., types 1 and 2) epithelial and endothelial cells in a rat model.[26] The effect was attenuated by pretreatment with a specific xanthine oxidase inhibitor. It seems likely that local ROS production by alveolar epithelial cells leads to apoptosis and damage to the blood–air barrier, leading to flooding of the alveolus with fluid and inflammatory cells (see box on page 535).

The Role of Neutrophils

Leukocyte infiltration is a crucial component of the cascade of IR injury. Platelet-activating factor, ROS, and xanthine oxidase are all chemotactic for neutrophils.[12] Leukocyte extravasation into tissues (or the alveoli) depends on integrin–immunoglobulin interactions involving adhesion molecules. Adhesion molecules are upregulated on pulmonary endothelial cells during ischemia.[23]

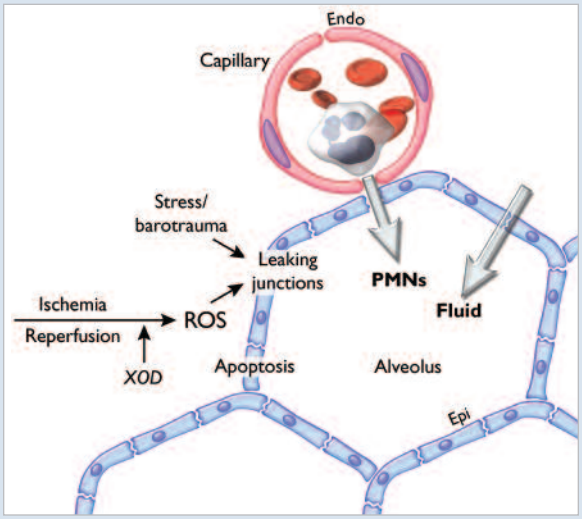
In a rabbit model,[17] both edema fluid and neutrophil accumulation within alveoli were reduced by pretreatment with dimethylthiourea; however, exogenous catalase was found to be ineffective, suggesting intracellular superoxide formation. Superoxide dismutase was subsequently found to delay neutrophilic effusion but ultimately did not prevent RPE.[27] Lodoxamide tromethamine, which reduces infarct size after reperfusion of ischemic myocardium, reduced the degree of both proteinaceous and neutrophilic exudation in a rabbit RPE model.[28]

Clinical and Comparative Aspects

As already noted, RPE is a well-documented, albeit rare condition in humans with pleural disease undergoing thoracic drainage of either air or fluid. Eighty-three percent of cases reported in one human study[4] were associated with drainage of a pneumothorax. Symptoms arose within 1 hour (and often immediately) after drainage in 64% of patients and within 24 hours in the remainder.[4] Matsuura et al[24] reported that RPE developed in 14% (21 of 146) of humans following drainage of spontaneous pneumothoraces and that the incidence of RPE increased in proportion to the extent of the pneumothorax. Some authors[1] have suggested that RPE occurs most often in humans when a chronically collapsed lung is rapidly reexpanded by increased negative intrapleural pressure. The importance of chronicity of collapse was supported in an

Case Study

A 5-year-old neutered domestic shorthaired cat presented for moderate dyspnea, tachypnea, and inappetence. The cat had been missing for 4 days and returned disheveled and weak. Radiographs of the thorax revealed loss of the diaphragmatic line and silhouetting of the cardiac border (**A**). A diagnosis of traumatic diaphragmatic herniation was made and celiotomy performed. Anesthesia was induced with propofol and maintained with isoflurane in oxygen via intermittent positive pressure ventilation. Because of equipment failure, a manometer was not available. At surgery, a ventral radial tear was located, through which the liver, spleen, and a section of small intestine had herniated. They were returned to the abdomen and considered normal via gross examination. The left caudal lung lobe was completely atelectatic. A thoracostomy tube was placed, and the herniorrhaphy and abdominal closure proceeded routinely. Most of the pleural air was removed via the tube at surgery. Initial recovery from anesthesia was unremarkable. Two hours after surgery, increased respiratory noises were noted, but the cat was not dyspneic. Twenty milliliters of free air was removed from the chest. Four hours after surgery, the cat's breathing was labored, and moist rales were auscultated bilaterally over the caudal thorax. No further air could be aspirated. A lateral radiograph (**B**) revealed a widespread alveolar pattern and a consolidated caudoventral lung lobe. Diuretic therapy (furosemide administered at 2 mg/kg IV) and nasal oxygen were initiated, but respiratory arrest occurred, and the cat died 8 hours after surgery. At the time of death, pink-stained serous fluid was in the trachea and flowed from the mouth, thereby confirming fatal pulmonary edema. We were unable to determine whether excessive airway pressure causing barotrauma or overly rapid removal of the pneumothorax affected the outcome.



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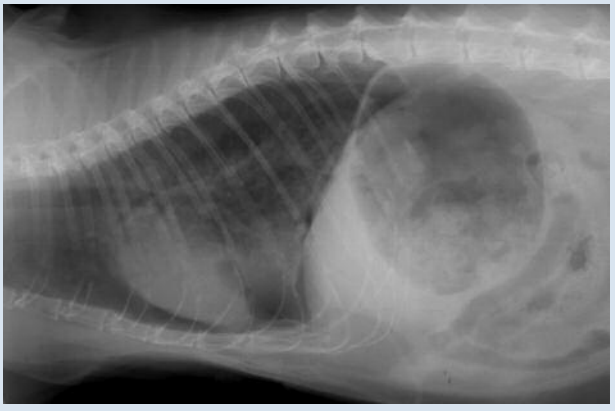
A. Diagram showing the proposed mechanism of IR-mediated injury to the blood–air barrier of the alveolus, resulting in reexpansion pulmonary edema. Reactive oxygen species (*ROS*) are formed under the action of xanthine oxidase (*XO*) when perfusion returns to atelectatic lung tissue. *ROS* leads to apoptosis and tight junction damage, allowing fluid from the interstitial and vascular spaces as well as inflammatory cell influx. The result is pulmonary edema. Mechanical shear stresses and barotrauma may also injure alveolar epithelial cells (*Epi*) or vascular endothelial cells (*Endo*). *PMNs* = polymorphonuclear neutrophils.



B. Lateral radiograph revealing a widespread alveolar pattern and consolidated caudoventral lung lobe.

experimental goat model in which 10 cm of water suction drainage led to gross evidence of RPE only after at least 72 hours of induced pneumothorax and lung collapse.[1] However, 17% of RPE cases in one medical review occurred despite the presence of lung collapse for less than 1 day, and in another 15%, pleural suction had not been used, leading Mahfood et al[4] to theorize that the rate of reexpansion might be more critical than the amount of air removed or the degree of suction applied. A clinical trial of small lumen catheter aspiration of human pneumothoraces, rather than large-diameter intercostal thoracostomy drainage, showed the technique to be effective, and no cases of RPE occurred in 40 patients treated in this manner.[29] Drainage of a pneumothorax resulting in RPE has also been reported in a dog.[30] Signs of respiratory distress arose within minutes

of rapid evacuation of approximately 500 ml of air from the thoracic cavity of the 46.2-lb (21-kg) patient. Pulmonary edema was confirmed radiographically, and the dog responded to symptomatic therapy.

Drainage of pleural effusions, pulmonary bullae, surgical removal of intrathoracic masses, surgically induced atelectasis, and video-assisted thoracoscopic surgery are other reported initiating events in humans[4,14,31]; however, to our knowledge, there is only one report of RPE after surgery for TDH (chronic) in the human literature.[32] RPE has been cited as a cause of postoperative death in small animals undergoing TDH repair, with cats seemingly at greater risk than dogs.[7,33,34] In one case series[33] reporting the outcomes of 56 dogs and cats presenting with TDH, 45% (five of 11) of postoperative deaths in cats in the study were attributed to RPE. In four of these cases, the herniation was chronic, with the duration of clinical signs ranging from 9 days to 6 weeks; however, the remaining cat had been injured only for 24 hours. Four cats died within hours of surgery and one the following day. The surgical technique used in all cases involved final closure of the diaphragmatic defect while using positive pressure ventilation to maximally expand the lungs, eliminating as much air as possible from the thorax. Based on these findings, Garson et al[33] suspected that overzealous reinflation pressure might be responsible for RPE and therefore recommended completing TDH surgery with an open chest drain in place, as had been done for the 33 dogs in their series, which was notably free of RPE mortalities. However, the average duration of clinical signs referable to TDH (and hence chronicity of herniation) was less than 5 days in dogs compared with 1 to 9 weeks in cats. Therefore, it could not be determined whether cats are more prone to RPE or the chronicity of the disease was the contributing factor. Removal of pleural fluid and formation of pulmonary edema were also associated with postoperative mortality in cats undergoing surgery for chronic TDH in a larger case series of 482 cats.[34]

Whereas rapid reestablishment of negative pressure seems to be associated with RPE in humans undergoing pleural space evacuation, barotrauma induced by mechanical ventilation may be the triggering event in the development of RPE in small animals undergoing surgery for TDH. RPE was confirmed via histology in a cat that died less than 3 hours following herniorrhaphy for TDH.[35] The method used to reinflate the lungs in this patient was rapid reexpansion via a combination of positive pressure ventilation and chest-tube aspiration at the time of diaphragmatic closure. Soon after, frothy fluid suggestive of pulmonary edema began to accumulate within the cat's endotracheal tube. A postoperative thoracic radiograph revealed air bronchograms and alveolar infiltrates, a distended trachea, and the presence of free air within the pleural space. The cat died approximately 2 hours later despite symptomatic and supportive therapy, including reintubation and application of IPPV. Fatal edema during recovery has also been reported after sternal splinting for pectus excavatum abnormality in a kitten.[36] A thoracotomy was not performed, but significant pulmonary atelectasis had been noted before surgery, during which the volume of the thorax was acutely expanded as the sternal defect was corrected. The kitten became dyspneic and cyanotic, with moist rales noted via thoracic auscultation shortly after sternal splinting, but responded to IPPV with 100% oxygen. However, within minutes, frothy, serosanguineous fluid was evident in the endotracheal tube. The fluid flow soon became copious, and the kitten had recurrent bouts of cyanosis despite ventilatory support, airway suction, and supportive treatment. The kitten was extubated when it would no longer tolerate an endotracheal tube and was placed in an oxygen cage but became dyspneic and experienced cardiopulmonary arrest soon after. We have seen fatal RPE develop in two domestic cats within hours of seemingly routine TDH repair. Both cats died from respiratory arrest and had pink-stained fluid draining from the lungs after death (see case study on page 535). In each patient, manual IPPV was performed throughout surgery, but forcible reexpansion during hernia closure was not performed. A small lumen thoracostomy tube was then used to remove air from the pleural space. Despite these measures, both cats developed RPE.

Reexpansion pulmonary edema and ischemia–reperfusion injury are potentially fatal complications in the postoperative period following correction of diaphragmatic herniation.

Surgical Recommendations

Available evidence suggests that rapid reexpansion of atelectatic lung lobes with excessive airway pressures can

result in reperfusion injury of collapsed vascular beds in small animals undergoing surgery for TDH. Barotrauma to lung parenchyma may compound IR injury, leading to potentially fatal infiltration of the alveolus with protein-rich fluid. Although veterinary surgical texts up until 1983 recommended completing closure of the diaphragmatic defect by tying the last suture during maximal assisted inflation (to reestablish negative intrathoracic pressure), current recommendations call for chronically atelectatic lungs to be reinflated only by gradual reexpansion.[37–42] Airway pressure should not exceed 15 to 20 cm of water pressure, particularly when there is evidence of lung damage.[38,39] This requires that airway pressures be monitored during manual IPPV or that if mechanical ventilators are used, they be operated correctly. Collapsed lung lobes that do not reinflate with 15 to 20 cm of water pressure should be left collapsed, and a chest drain should then be inserted. A standard thoracostomy tube can be placed under direct visualization during herniorrhaphy, or a small tube drain can be placed through the diaphragmatic rent and out through an abdominal wall stab incision.[42,43] Intermittent suction drainage by syringe should result in these lung lobes gradually reexpanding over several hours. Animals with significant preoperative lung collapse should be recovered with a pneumothorax while being closely observed for signs of dyspnea or poor oxygenation. More air should be drawn off, as needed, in a gradual fashion over 8 to 12 hours via the drain.[6,33,41] The rate of drainage has not been determined in a clinical trial, and this recommendation remains empirical. The drain should remain in place for another 12 hours and intermittently checked for the presence of pneumothorax or hemothorax secondary to lung reexpansion.[33,40]

Therapy for Ischemia–Reperfusion Injury

There is great interest in the development of therapeutic drugs to counter IR injury. Research has centered on blocking ROS formation, identifying ROS scavengers, blocking neutrophils, and preventing platelet activation. Many successful in vitro therapies require pretreatment and are therefore not always applicable in a clinical setting. RPE in TDH may represent a unique opportunity to intervene before the deleterious effect of reperfusion. Only some of the numerous agents that have undergone evaluation are mentioned here; a more in-depth discussion was recently provided by McMichael and Moore.[44] Dimethyl sulfoxide is a hydroxyl scavenger that inhibits prostaglandins, reduces platelet aggregation, and interferes with neutrophil chemotaxis and arachidonate metabolism. However, it also readily forms methyl radicals, which lead to harmful chain reactions and undesirable side effects.[11] Allopurinol (a free radical inhibitor) has shown benefit in several rodent models but was not shown to significantly affect outcome in an experimental canine GDV model.[45] Lack of efficacy was attributed to dogs having less xanthine oxidase activity than did rodents. Other canine models have shown allopurinol to be effective in limiting hepatic necrosis after experimentally induced GDV, but lack of a suitable commercial formulation has limited its clinical use.[46] It is currently available in tablet form as a therapy for gout in humans.

Pretreatment with deferoxamine (desferrioxamine), an iron chelator, increased survival in dogs in a GDV model.[47] Absorption and distribution of deferoxamine are significantly delayed if the drug is given intramuscularly; however, if it is given intravenously, it must be administered slowly (over at least 5 minutes) to avoid an adverse reaction.[48] Deferoxamine is available as an injection for iron overdose (in humans), and the suggested dose rate is 50 mg/kg for IR injury following GDV.[48]

The lazaroid (21-aminosteroid) tirilazad mesylate is a novel inhibitor of lipid membrane peroxidation induced by ROS. In animal models of subarachnoid hemorrhage, central nervous system trauma, and cerebral ischemia, the drug has been shown to limit the extent of secondary tissue damage, thus improving functional recovery. However, use of tirilazad mesylate failed to improve functional outcome in a rabbit model[49] of IR injury. Use of vitamins as antioxidants has also been extensively examined. In a porcine pulmonary reperfusion model,[50] vitamins C and E inhibited neutrophil activation but were not able to prevent oxygen radical production. A combined approach using preconditioning with ascorbate, vitamins A and E, and lecithinized superoxide dismutase has been suggested for use in human transplant surgery to decrease ischemic damage.[51] Prostaglandin (i.e., PGE_1) has been shown to reduce IR injury in animal models of lung transplantation, an effect that may be mediated by vasodilatory or antiinflammatory effects.[23] Whether PGE_1 would be efficacious in clinical cases of RPE secondary to TDH is unknown.

Spinal cord injuries have a secondary phase of injury beyond the inciting trauma, which is thought to be mediated at least in part by oxyradical production. Wide-scale human clinical trials reportedly show clinical improvement in acute spinal cord trauma patients treated within 8 hours with high-dose methylprednisolone (30 mg/kg IV), although recent reviews have

cast doubt on their validity.[52] High-dose methylprednisolone sodium succinate (20 to 30 mg/kg IV) has been recommended for acute spinal cord trauma in small animal patients.[53] Pretreatment with steroids before allowing reperfusion may be desirable. However, secondary spinal cord injury differs from IR injury secondary to strangulation of a herniated organ; therefore, the same dose recommendations cannot be made. In cases of gross tissue ischemia with thrombi in the supplying mesenteric vessels, amputation of the affected tissue should be considered. At this time, no single agent has been shown to ameliorate IR injury completely.[44]

CONCLUSION

The twin dangers of RPE and IR injury can make surgical management of TDH in companion animals challenging. Until greater insight into the pathogenesis of RPE is gained, only empirical recommendations can be made. During IPPV, careful monitoring of airway pressures is essential to avoid barotrauma. At the conclusion of herniorrhaphy, the anesthetist performing IPPV should not attempt to fully reinflate the collapsed lung and expel pleural air. Instead, a chest drain (thoracostomy tube) should be placed and sufficient pleural air evacuated to establish normal oxygen saturation, but not to the point that chronically collapsed lung lobes are reinflated. The remaining air should be drawn off intermittently in the postoperative period.

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ARTICLE #3 CE TEST

This article qualifies for 2 contact hours of continuing education credit from the Auburn University College of Veterinary Medicine. ***Paid subscribers may purchase individual CE tests or sign up for our annual CE program.*** *Those who wish to apply this credit to fulfill state relicensure requirements should consult their respective state authorities regarding the applicability of this program. To participate, fill out the test form inserted at the end of this issue or take CE tests online and get real-time scores at* ***CompendiumVet.com****. Test answers are available online free to paid subscribers as well.*

1. Which statement regarding reperfusion injury is incorrect?
a. In humans, RPE can occur following drainage of a pneumothorax.
b. Chronicity of lung collapse has been implicated as a factor in the development of RPE.
c. The rapidity of drainage and restoration of negative pressure have been implicated as factors in the development of RPE.
d. RPE is common in companion animals after herniorrhaphy for TDH.
e. Cats appear to be at greater risk of developing RPE than do dogs.

2. Which has not been implicated in the pathogenesis of RPE?
a. neutrophilic infiltration through damaged endothelial linings
b. oxyradical production via xanthine oxidase pathways
c. macrophages sequestering in the perialveolar interstitium
d. hypoxic insult leading to endothelial vascular damage
e. negative pulmonary interstitial pressures or barotrauma promoting increased fluid filtration from lung capillaries

3. Which statement regarding RPE in humans is incorrect?
a. RPE is a rare but well-recognized disease entity in humans.
b. Drainage of a pneumothorax is the most common initiating event.
c. Ventilatory assistance with positive end-expiratory pressure decreases mortality in serious cases.
d. Rapidity of pleural drainage has been implicated as a causal factor.
e. TDH is a common cause of RPE.

4. Which is a current recommendation(s) to lessen the risk for RPE following surgery to correct TDH?
a. IPPV should not be used to fully reinflate a collapsed lung and expel pleural air at the point of closure of the diaphragm.
b. A chest drain (thoracostomy tube) should be placed.
c. The animal should be recovered with a pneumothorax while being closely observed for signs of dyspnea or poor oxygenation.
d. After surgery, the pneumothorax should be alleviated over 8 to 12 hours via the drain.
e. all of the above

5. Conditions that promote the development of reperfusion injury include
a. GDV.
b. collapse and lack of ventilation of pulmonary parenchyma.
c. strangulation of viscera through a hernia.
d. all of the above
e. none of the above

6. Which statement regarding the proposed mechanisms of IR is correct?
a. When oxygenated blood ceases to flow through tissue, cell metabolism becomes largely aerobic.
b. Returning strangulated organs to the abdomen allows reperfusion of stagnant capillary beds and sinusoids.
c. Liberation of metabolites that damage endothelial linings is an unlikely result of IR injury.

(CE Test continues on next page)

Article #3 CE Test *(continued from p. 539)*

d. The extent of reflow is proportional to the duration of the ischemia.
e. Inflow (arterial) obstruction appears to be more problematic than does outflow obstruction.

7. Which statement regarding production of oxyradicals and membrane injury is incorrect?
a. During periods of ischemia, hypoxanthine accumulates from the degradative pathway of ATP.
b. Xanthine oxidase oxidizes hypoxanthine, generating superoxide radicals.
c. Superoxide radicals are dismutated to H_2O_2 by superoxide dismutase.
d. H_2O_2 is a potent free radical.
e. OH^- radicals interact with membrane lipids to form self-perpetuating chains of toxic hydroperoxides.

8. Drug treatments investigated in the treatment of IR include
a. deferoxamine.
b. dimethyl sulfoxide.
c. chymopapain.
d. allopurinol.
e. a, b, and d

9. Which statement regarding corticosteroid therapy for spinal cord injury is incorrect?
a. Spinal cord injury is thought to be mediated at least in part by oxyradical production.
b. Initiation of steroid therapy after 8 hours is unlikely to be efficacious.
c. Methylprednisolone sodium succinate is used at high doses (20 to 30 mg/kg IV).
d. Standard doses (0.5 to 1 mg/kg IV) of methylprednisolone sodium succinate are recommended.
e. The goal of therapy is to achieve a free radical scavenging effect.

10. Which statement regarding lazaroids is incorrect?
a. Lazaroids may inhibit lipid membrane peroxidation.
b. Lazaroids may limit the extent of secondary tissue damage induced by subarachnoid hemorrhage.
c. Tirilazad mesylate improved functional outcome in a model of IR injury.
d. As free radical scavengers, lazaroids act similar to vitamins A and E.
e. Lazaroids may limit the extent of secondary tissue damage induced by cerebral ischemia.